New Combigan™

(brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5%

AMCP DOSSIER

December, 2007

ALLERGAN

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GLOSSARY OF TERMS

AE	adverse event
AHFS	American Hospital Formulary Service
AHP	aqueous humor production
ALT	argon laser trabeculoplasty
AUC	area under the curve
AWP	average wholesale price
BAK	benzalkonium chloride
BID	twice daily
CAI	carbonic anhydrase inhibitor
cAMP	cyclic adenosine monophosphate
CEED	COMBIGAN™ Early Experience Data
CD-1	cluster designation
CF	count fingers
CHO	Chinese Hamster Ovary
CI	confidence interval
CNS	Central nervous system
FDA	Federal Drug Administration
HIPS	High impact polystyrene
HTA	health technology assessment
ICD-9	International Classification of Diseases, Version 9
IOP	intraocular pressure
ITT	intent-to-treat
LDPE	Low density polyethylene
LOCF	last observation carried forward
MAOI	monoamine oxidase inhibitor
NDA	new drug application
NDC	national drug code
NLP	no light perception
ODB	Ontario drug benefit
OHT	ocular hypertension
OU	oculus uterque
POAG	primary open-angle glaucoma
PXE	primary exfoliation syndrome
QoL	quality of life
RAMQ	Régie de l'assurance maladie du Québec
RCT	Randomized Control Trial
SD	standard deviation
SE	standard error
SLT	selective laser trabeculoplasty
TID	three times daily
TTO	time trade off
QD	once daily
US	United States
UK	united kingdom
WAC	wholesale acquisition cost

1 PRODUCT INFORMATION

1.1 Product Description

1.1.1 Product Profile

Trade name: COMBIGAN™

Generic name: (brimonidine tartrate / timolol maleate ophthalmic solution) 0.2% / 0.5%

Presentation: In solution, COMBIGAN™ (brimonidine tartrate / timolol maleate ophthalmic solution) 0.2%/0.5% has a clear, greenish-yellow color. It has an osmolality of 260-330 mOsmol/kg and a pH during its shelf life of 6.5 – 7.3. COMBIGAN™ is supplied in both a 5mL and 10mL dropper bottles.

NDA: 21-398

Therapeutic class: Eye preparations - Glaucoma preparations.

FDA approval: October 31, 2007

Indication: **COMBIGAN™** (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% is an alpha adrenergic receptor agonist with a beta adrenergic receptor inhibitor indicated for the reduction of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP; the IOP-lowering of **COMBIGAN™** dosed twice a day was slightly less than that seen with the concomitant administration of 0.5% timolol maleate ophthalmic solution dosed twice a day and 0.2% brimonidine tartrate ophthalmic solution dosed three times per day.

Recommended Dose: One drop in the affected eye(s) twice daily, approximately 12 hours apart. If more than one topical ophthalmic product is to be used, the different products should be instilled at least 5 minutes apart.

1.1.2 Dosage forms, NDC and WAC

COMBIGAN™ is supplied sterile, in white opaque plastic LDPE bottles and tips, with blue high impact polystyrene (HIPS) caps as follows:

Volume of Medication	Bottle Size	NDC	WAC
5 mL	10 mL	0023-9211-05	$56.61
10 mL	10 mL	0023-9211-10	$113.22

1.1.3 Copy of the official product labeling/literature

See enclosed Full Prescribing Information

1.1.4 AHFS Drug Classification

Alpha Adrenergic Receptor Agonist/Beta-Adrenergic Receptor Blocking Agent

1.1.5 Pharmacological Action

Mechanism of Action:

COMBIGAN™ ophthalmic solution is comprised of two components: brimonidine tartrate and timolol. Each of these two components decreases elevated intraocular pressure, whether or not associated with glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous field loss and optic nerve damage.

COMBIGAN™ is a selective alpha-2 adrenergic receptor agonist with a non-selective beta-adrenergic receptor inhibitor. Both brimonidine and timolol have a rapid onset of action, with peak ocular hypotensive effect seen at two hours post-dosing for brimonidine and one to two hours for timolol. [1, 2]

Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action by reducing aqueous humor production and increasing nonpressure dependent uveoscleral outflow.

Timolol maleate is a $beta_1$ and $beta_2$ adrenergic receptor inhibitor that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity.

1.1.6 Pharmacodynamics and Pharmacokinetics

Systemic absorption of brimonidine and timolol was assessed in healthy volunteers and patients following topical dosing with COMBIGAN™. Normal volunteers dosed with one drop of COMBIGAN™ ophthalmic solution twice daily in both eyes for seven days showed peak plasma brimonidine and timolol concentrations of 30 pg/ml and 400 pg/ml, respectively. Plasma concentrations of brimonidine peaked at1 to 4 hours after ocular dosing and declined with a systemic half-life of approximately 3 hours. Peak plasma concentrations of timolol occurred in about 1 to 3 hours post-dose with an apparent systemic half-life about 7 hours after ocular administration.

In a crossover study of COMBIGAN™, brimonidine tartrate 0.2%, and timolol 0.5% administered twice daily for 7 days in healthy volunteers, the mean brimonidine area-under-the-plasma-concentration-time curve (AUC) for COMBIGAN™ was 128 ± 61 pg•hr/mL versus 141 ± 106 pg•hr/mL for the respective monotherapy treatments; mean C_{max} values of brimonidine were comparable following COMBIGAN™ treatment versus monotherapy (32.7 ± 15.0 pg/mL versus 34.7 ± 22.6 pg/mL, respectively). Mean timolol AUC for COMBIGAN™ was similar to that of the respective monotherapy treatment (2919 ± 1679 pg•hr/mL versus 2909 ± 1231 pg•hr/mL, respectively); mean C_{max} of timolol was approximately 20% lower following COMBIGAN™ treatment versus monotherapy.

In a parallel study in patients dosed twice daily with COMBIGAN™, twice daily with timolol 0.5%, or three times daily with brimonidine tartrate 0.2%, one-hour post dose plasma concentrations of timolol and brimonidine were approximately 30-40% lower with COMBIGAN™ than their respective monotherapy values. The lower plasma brimonidine concentrations with COMBIGAN™ ophthalmic solution appears to be due to twice-daily dosing for COMBIGAN™ versus three-times dosing with brimonidine tartrate 0.2%.

1.1.7 Clinical Evaluations:

Clinical studies were conducted to compare the IOP-lowering effect over the course of the day of **COMBIGAN™** administered twice a day (BID) to individually-administered brimonidine tartrate ophthalmic solution, 0.2% administered three times per day (TID) and timolol maleate ophthalmic solution, 0.5% BID in patients with glaucoma or ocular hypertension. **COMBIGAN™** BID provided an additional 1 to 3 mm Hg decrease in IOP over brimonidine treatment TID and an additional 1 to 2 mm Hg decrease over timolol treatment BID during the first 7 hours post dosing. However, the IOP-lowering of **COMBIGAN™** BID was less (approximately 1-2 mm Hg) than that seen with the concomitant administration of 0.5% timolol BID and 0.2% brimonidine tartrate TID. **COMBIGAN™** administered BID had a favorable safety profile versus concurrently administered brimonidine TID and timolol BID in the self-reported level of severity of sleepiness for patients over age 40.

1.1.8 Contraindications

COMBIGAN™ ophthalmic solution is contraindicated in patients with: (1) bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease; (2) sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, cardiogenic shock, and (3) hypersensitivity to any component of this product. (CONTRAINDICATIONS section)[2]

1.1.9 Warnings/Precautions

Potentiation of Respiratory Reactions including Asthma

COMBIGAN™ contains timolol maleate; and although administered topically can be absorbed systemically. Therefore, the same types of adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions including death due to bronchospasm in patients with asthma have been reported following systemic or ophthalmic administration of timolol maleate. (CONTRAINDICATIONS section)[2]

Cardiac Failure

Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, COMBIGAN™ ophthalmic solution should be discontinued.(CONTRAINDICATIONS section)[2]

Obstructive Pulmonary Disease

Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma, in which COMBIGAN™ is contraindicated) should, in general, not receive beta-blocking agents, including COMBIGAN™. (CONTRAINDICATIONS section)[2]

Potentiation of Vascular Insufficiency

COMBIGAN™ may potentiate syndromes associated with vascular insufficiency. COMBIGAN™ should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans

Increased Reactivity to Allergens

While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or

therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

Potentiation of Muscle Weakness

Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

Masking of Hypoglycemic Symptoms in Patients with Diabetes Mellitus

Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Masking of Thyrotoxicosis

Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

Contamination of Topical Ophthalmic Products After Use

There have been reports of bacterial keratitis associated with the use of multiple dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Impairment of Beta-adrenergically Mediated Reflexes During Surgery

The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

Drug Interactions

Antihypertensives/Cardiac glycosides: Because COMBIGAN™ may reduce blood pressure, caution in using drugs such as antihypertensives and/or cardiac glycosides with COMBIGAN™ is advised.

Beta-adrenergic blocking agents: Patients who are receiving a beta-adrenergic blocking agent orally and COMBIGAN™ ophthalmic solution should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Calcium antagonists: Caution should be used in the co-administration of beta-adrenergic blocking agents, such as COMBIGAN™, and oral or intravenous calcium antagonists because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, co-administration should be avoided.

Catecholamine-depleting drugs: Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

CNS Depressants: Although specific drug interaction studies have not been conducted with COMBIGAN™, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered.

Digitalis and calcium antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

CYP2D6 inhibitors: Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g., quinidine, SSRIs) and timolol.

Tricyclic Antidepressants: Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with COMBIGAN™ ophthalmic solution in humans can lead to resulting interference with the IOP lowering effect. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

Monoamine oxidase inhibitors: Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine and potentially result in an increased systemic side-effect such as hypotension. Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

With brimonidine tartrate, no compound-related carcinogenic effects were observed in either mice or rats following a 21-month and 24-month study, respectively. In these studies, dietary administration of brimonidine tartrate at doses up to 2.5 mg/kg/day in mice and 1 mg/kg/day in rats achieved 150 and 210 times, respectively, the plasma C_{max} drug concentration in humans treated with one drop COMBIGAN™ into both eyes twice daily, the recommended daily human dose.

In a two-year study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day [approximately 25,000 times the maximum recommended human ocular dose of 0.012 mg/kg/day on a mg/kg basis (MRHOD)]. Similar differences were not observed in rats administered oral doses equivalent to approximately 8,300 times the daily dose of COMBIGAN™ in humans.

In a lifetime oral study of timolol maleate in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day, (approximately 42,000 times the MRHOD), but not at 5 or 50 mg/kg/day (approximately 420 to 4,200 times higher, respectively, than the MRHOD). In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

Brimonidine tartrate was not mutagenic or clastogenic in a series of in vitro and in vivo studies including the Ames bacterial reversion test, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, and three in vivo studies in CD-1 mice: a host-mediated assay, cytogenetic study, and dominant lethal assay.

Pregnancy

Pregnancy Category C: Teratogenicity studies have been performed in animals.

Brimonidine tartrate was not teratogenic when given orally during gestation days 6 through 15 in rats and days 6 through 18 in rabbits. The highest doses of brimonidine tartrate in rats (1.65 mg/kg/day) and rabbits (3.33 mg/kg/day) achieved AUC exposure values 580 and 37-fold higher,

respectively, than similar values estimated in humans treated with COMBIGAN™, 1 drop in both eyes twice daily.

Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day [4,200 times the recommended human ocular dose of 0.012 mg/kg/day on a mg/kg basis (MRHOD)] demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (83,000 times the MRHOD) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses 8,300 times the MRHOD without apparent maternotoxicity.

There are no adequate and well-controlled studies in pregnant women; however, in animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. Because animal reproduction studies are not always predictive of human response, COMBIGAN™ should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers

Timolol has been detected in human milk following oral and ophthalmic drug administration. It is not known whether brimonidine tartrate is excreted in human milk, although in animal studies, brimonidine tartrate has been shown to be excreted in breast milk. Because of the potential for serious adverse reactions from COMBIGAN™ ophthalmic solution in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

COMBIGAN™ is not recommended for use in children under the age of 2 years. During post-marketing surveillance, apnea, bradycardia, hypotension, hypothermia, hypotonia, and somnolence have been reported in infants receiving brimonidine. The safety and effectiveness of brimonidine tartrate and timolol maleate have not been studied in children below the age of two years.

The safety and effectiveness of COMBIGAN™ have been established in the age groups 2 – 16 years of age. Use of COMBIGAN™ in these age groups is supported by evidence from adequate and well-controlled studies of COMBIGAN™ ophthalmic solution in adults with additional data from a study of the concomitant use of brimonidine tartrate ophthalmic solution 0.2% and timolol maleate ophthalmic solution in pediatric glaucoma patients (ages 2 to 7 years). In this study, brimonidine tartrate ophthalmic solution 0.2% was dosed three times a day as adjunctive therapy to beta-blockers. The most commonly observed adverse reactions were somnolence (50%-83% in patients 2 to 6 years) and decreased alertness. In pediatric patients 7 years of age or older (>20 kg), somnolence appears to occur less frequently (25%). Approximately 16% of patients on brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence.

Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

1.1.10 Adverse Events

In clinical trials of 12 months duration with COMBIGAN™, the most frequent reactions associated with its use occurring in approximately 5% to 15% of the patients included: allergic conjunctivitis, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, ocular burning, and stinging. The following adverse reactions were reported in 1% to 5% of patients: asthenia, blepharitis, corneal erosion, depression, epiphora, eye discharge, eye dryness, eye irritation, eye pain, eyelid edema, eyelid erythema, eyelid pruritus, foreign body sensation, headache, hypertension, oral dryness, somnolence, superficial punctate keratitis, and visual disturbance.

1.1.11 Overdose

No information is available on overdosage with COMBIGAN™ ophthalmic solution in humans. There have been reports of inadvertent overdosage with timolol ophthalmic solution resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

1.1.12 Dosing and Administration

The recommended dose is one drop of COMBIGAN™ in the affected eye(s) twice daily approximately 12 hours apart. If more than one topical ophthalmic product is to be used, the different products should be instilled at least 5 minutes apart. COMBIGAN™ ophthalmic solution is supplied sterile in white opaque plastic LDPE bottles and tips with blue high impact polystyrene (HIPS) caps in 5 mL , and 10 mL bottles.

1.1.13 Co-administered Therapies

In a small proportion of patients treatment with more than two topical anti-glaucoma products may be required.[3] COMBIGAN™ is indicated for the reduction of IOP in patients with chronic open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical β-blockers.[4] COMBIGAN™ may be used adjunctively with other second line anti-glaucoma products, e.g., prostaglandins.

COMBIGAN™ ophthalmic solution may also be administered concomitantly with other topical ophthalmic medications, including corticosteroids to treat inflammation, antibiotics to treat infection, and lubricating drops for dry eye syndrome.

1.1.14 Differences between COMBIGAN™ and *Cosopt*®

Table 1. Differences between COMBIGAN™ and *Cosopt*®

	COMBIGAN™	***Cosopt*®**
Pharmacological class	Alpha-adrenergic receptor agonist with a beta-adrenergic receptor inhibitor	Beta-adrenergic receptor blocking agent.and carbonic anhydrase inhibitor (CAI)
Indication and Usage	**COMBIGAN™** (brimonidine tartrate/ timolol maleate ophthalmic solution) 0.2%/0.5% is an alpha adrenergic receptor agonist with a beta adrenergic receptor inhibitor indicated for the reduction of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP; the IOP-lowering of **COMBIGAN™** dosed twice a day was slightly less than that seen with the concomitant administration of 0.5% timolol maleate ophthalmic solution dosed twice a day and 0.2% brimonidine tartrate ophthalmic solution dosed three times per day.	***Cosopt*®** is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers (failed to achieve target IOP determined after multiple measurements over time). The IOP lowering of Cosopt b.i.d. was slightly less than that seen by concomitant administration of 0.5% timolol b.i.d. and 2.0% dorzolamide t.i.d.
Mechanism of Action	Dual mechanism of action–reduces aqueous humor production and increases nonpressure-dependent uvescleral outflow	Reduces aqueous humor production.
Dosage and Administration	• One drop in the affected eye(s) twice daily, approximately 12 hours apart • If more than 1 topical ophthalmic product is to be used, the drugs should be administered at least 5 minutes apart	• One drop in the affected eye(s) twice daily • If more than 1 topic ophthalmic drug is being used, the drugs should be administered at least 10 minutes apart

Most Common Adverse Reactions	The most common adverse reactions associated with COMBIGAN™ use occurring in approximately 5% to 15% of patients included allergic conjunctivitis, conjunctival folliculosis, conjuctival hyperemia, eye pruritus, and ocular burning and stinging	Approximately 5% of all patients discontinue therapy with ***Cosopt®*** because of adverse reactions. The most frequently reported adverse events were taste perversion (bitter, sour, or unusual taste) or ocular burring and/or stinging in up to 30% of patients. Conjunctival hyperemia, blurred vision, superficial punctuate keratitis or eye itching were reported between 5% to 15% of patients.
How Supplied	White, opaque plastic LDPE bottles and tips with blue high-impact polystyrene(HIPS) caps in 5-mL and 10-ml sizes.	*Ocumeter® Plus* container; White, translucent, HDPE plastic ophthalmic dispenser with a controlled drop tip and a white polystyrene cap with dark blue label in 10- ml size only.

1.2 Place of the Product in Therapy

1.2.1 Epidemiology and Relevant Risk Factors

Glaucoma refers to a group of eye disorders characterized by progressive optic neuropathy and visual field loss. Along with age-related macular degeneration, cataracts and diabetic neuropathy, it is one of the four most frequent causes of chronic visual impairment in the elderly. Primary open-angle glaucoma (POAG) is the most common form of the disease. The prevalence of POAG increases with advancing age.[5] Glaucoma (POAG) has a significant impact on the quality of life of the affected individuals and imposes a substantial economic burden on society.[4]

POAG is estimated to affect 2.22 million individuals in the U.S.[6] With the aging of the population, the number of people with POAG is expected to increase by 50% by the year 2020.[6] Blacks have nearly three times the age-adjusted prevalence as do whites.[6] In addition to being a risk factor for the disease, black race is also associated with earlier age of onset, rapid disease progression, and increased likelihood of irreversible blindness in patients with POAG.[7]

Ocular hypertension (OHT) or elevated intraocular pressure (IOP) >21 mm Hg is the most important risk factor for glaucoma; to date there is no evidence that any other method of treatment other than lowering IOP has any effect on the progression of POAG. Continued advances in laser and incisional surgery notwithstanding, medical therapy remains the primary means of controlling IOP. The glaucoma treatment armamentarium comprises several classes of topical agents; however, all lower IOP either by decreasing the production of aqueous humor (e.g. β-blockers, carbonic anhydrase inhibitors), increasing its outflow (e.g. prostaglandin analogue), or both (e.g. α_2-adrenergic agonists).[4]

1.2.2 Pathophysiology

Glaucoma is a disease of the optic nerve which is often associated with elevated IOP. Nerve fibers from the optic nerve may become pinched where they exit the eye, causing death of these fibers and reduction of retinal ganglion cells. This damage to the optic nerve is progressive and leads to thinning of the neural rim, enlargement of the optic nerve cup, and optic nerve atrophy. It is this loss of nerve fibers that leads to permanent deficits in the visual field.[8] It is presumed that elevated IOP, caused by increased aqueous humor in the eye, often leads to this optic nerve damage. In the normal eye, aqueous humor, which fills the anterior and posterior chambers, is produced by the ciliary body and drained through the trabecular meshwork. In POAG, IOP is elevated due to a dysfunction of the drainage system.[8] The rate of development of optic nerve damage from elevated IOP is approximately 1% per year.[8] However, elevated IOP is not pathognomonic for glaucoma; more than two thirds of individuals with elevated IOP (>21 mmHg) do not develop glaucomatous changes of the optic nerve, and 15% of POAG are in people with normal IOP (normal tension glaucoma, NTG). [8]

1.2.3 Clinical Presentation

POAG rarely causes symptoms in patients. A loss of more than 40% of optic nerve fibers will occur before a patient becomes aware of the loss of peripheral vision, or "tunnel vision." Therefore, POAG is usually an incidental finding during an ophthalmology exam performed for other reasons. With direct ophthalmoscopy, a cup-to-disc ratio of >0.5, a ratio asymmetry of >0.2 between both eyes, or a highly asymmetric ratio in one eye are all signs of glaucomatous damage. These signs are often detectable before visual field loss occurs.[8]

The rate of progression of glaucoma varies considerably among patients. There are certain risk factors that are known to speed up the deterioration in the visual field, such as elevated IOP, increasing age, and certain systemic diseases. In a study of 177 patients, untreated glaucoma took an average of 14.4 years to progress from early to end stage (i.e., legal blindness) at IOPs between 21 to 25 mmHg, 6.5 years for IOPs between 26 to 30 mmHg; and 2.9 years for IOPs above 30 mmHg.[9]

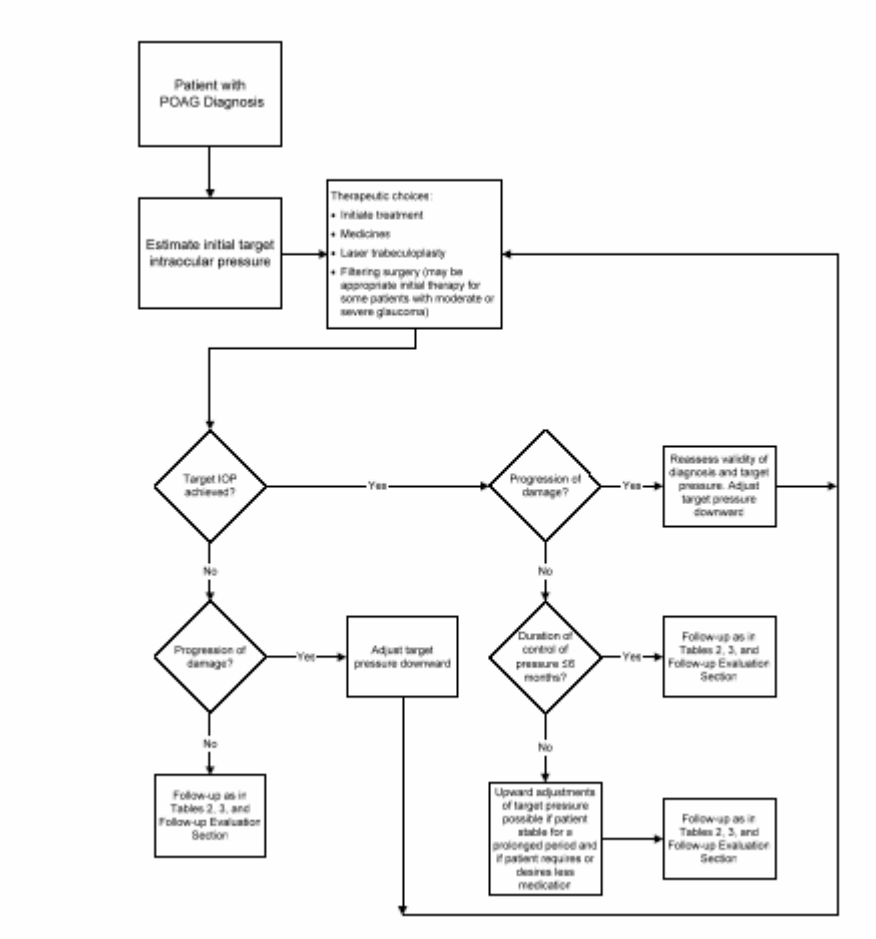
1.2.4 Approaches to Treatment

A number of clinical trials have shown that a reduction of IOP reduces the rate of progression of POAG.[10] Current recommendations are to decrease IOP by 20% in patients with OHT at risk of POAG, by 30% in early-to-moderate POAG, and by 40-50% in severe POAG.[10] However, due to inter-individual variability in the effect of IOP on the optic nerve, patients should be monitored regularly with visual field perimetry and optic disc photography to detect disease progression. If there is progression despite reaching the target IOP, IOP should be decreased by an additional 15%.[10]

The three approaches used for reducing IOP are pharmacologic therapy, laser surgery, and conventional surgery. Pharmacologic treatments (as monotherapy or in combination) are most often used first-line because they are considered safer than the surgical therapies. Likewise, laser trabeculoplasty is usually considered before the more invasive trabeculectomy (**Figure 1**).[3]

Pharmacotherapy usually begins with a single topical agent; while this has traditionally been a β-blocker, increasingly a prostaglandin analogue is used as a first line agent. Due to the chronic nature of glaucoma, patients on monotherapy frequently require additional agents to achieve adequate IOP control. When dual therapy is indicated, fixed combinations of ocular hypotensive agents have several potential advantages over concomitant therapy with the same two drugs. Because they are easier to administer, fixed combination eyedrops may be a more convenient treatment, potentially improving compliance as well as the efficiency of drug delivery. Fixed combination products also limit the amount of preservative applied to the eye, potentially improving tolerability as well as eventual surgical outcomes in patients who ultimately require filtering procedures.[4]

Figure 1. Algorithm for the Management of Patients with Primary Open-Angle Glaucoma
Preferred Practice Pattern, Primary Open Angle Glaucoma, American Academy of Ophthalmology® Copyright © 2005.



Pharmacologic Treatment

A number of classes of IOP-lowering medications are available; although they work through different mechanisms, they all reduce IOP by decreasing aqueous production and/or increasing aqueous outflow **(Table 2).** The exact mechanisms by which this is accomplished may differ between classes.[10] When prescribing initial medical therapy for glaucoma or ocular hypertension, there are a number of factors to consider.

Table 2. Mechanism of Action of Glaucoma Medications[10]

	Decrease aqueous production	Increase aqueous outflow
Prostaglandin derivatives		X
Beta-Antagonists	X	
Alpha-Agonists (strengthen)	X	X
Carbonic Anhydrase Inhibitors	X	
Cholinergic Agonists		X
COMBIGAN™	X	X
Cosopt™	X	

The choice of medical therapy depends ultimately on efficacy, safety and tolerability (both ocular and systemic), and cost. Because of inter-patient variability in response to medications for both efficacy and adverse events, it may be necessary to try a few medication classes before finding the right one for each individual patient.[3] It is also considered ideal to have a patient on a single effective medication, as opposed to multiple medications for additive effects, due to the impracticality of polypharmacy.[3] However, if a patient's IOP is not adequately controlled on a single medication, then adjuvant medication should be added to the regimen, preferably one that lowers IOP through a different mechanism than the first medication.

Initial monotherapy fails to control IOP within the first 2 years of treatment in as many as 50% of glaucoma patients in the United States. The recent Ocular Hypertension Treatment Study randomized patients to observation or treatment arm in which the therapeutic goal was a modest 20% IOP reduction. In the study, 40% of patients randomized to treatment required more than one medication to achieve the 20% reduction goal.[11] For patients who require multidrug regimens to control IOP adequately, fixed combinations offer convenience, efficacy, and safety. There often exist treatment disincentives: medications are costly, time-consuming to instill, and have side effects that are often perceived by the patient as being worse than the glaucoma before treatment.[11]

Fixed combinations of glaucoma medications offer patients a reduction in the number of bottles of medication they must purchase, which can represent a cost savings for patients whose drug plan requires a per-bottle copayment. Fixed combinations also represent a reduction in the number of drops per day they are required to instill. An established washout effect resulting from rapid-sequence instillation of multiple medications requires that patients wait approximately 5 minutes between eye drops. Fixed combinations offer a reduced time commitment for drop instillation and the potential for greater efficacy by eliminating the washout effect. The cost savings and time savings may help enhance compliance.[11] Finally, having two therapies in one drop decreases exposure to preservatives, which may increase tolerability.[11]

The available fixed combination products currently all contain the beta-blocker timolol 0.5%, and are indicated when adequate IOP control is not achieved via beta-blocker monotherapy. In published studies, *Cosopt*®, a combination of timolol 0.5% and dorzolamide 2%, has demonstrated a potentially greater IOP-lowering effect compared with concomitant therapy. Other investigative combinations in research include timolol and prostaglandins.[11]In a recent

multicenter study of COMBIGAN™ ophthalmic solution, the fixed combination of brimonidine and timolol, provided statistically significantly better IOP-lowering efficacy than did either component used as monotherapy. This was seen in the evaluation of mean change from baseline IOP and the evaluation of mean IOP.[12]

The Pharmacodynamic profile of COMBIGAN™ in the treatment of glaucoma and OHT offers one of it's components, brimonidine which lowers IOP by a dual mechanism of action, involving a reduction in aqueous humor production and an increase in aqueous humor outflow via the uveoscleral pathway.[13] In comparison, the other component, timolol exerts its ocular hypotensive effect solely by reducing aqueous humor formation.[4] In a randomized, double-masked, placebo-controlled study in 20 healthy volunteers, the reduction in aqueous humor production (AHP; 58.9%) and IOP (34.7%) observed following coadministration of separate topical formulations of brimonidine 0.2% and timolol 0.5% were numerically greater than those seen after instillation of brimonidine (AHP 33.1%; IOP 20.3%) or timolol (AHP 49.9%; IOP 22.9%) alone.[4]

FDA approval of COMBIGAN™ ophthalmic solution further demonstrates the widespread practice of adjunctive usage of IOP-lowering agents and the need to optimize such usage.

Diseases that require dosing medications on a rigorous schedule are fraught with issues of adherence. In general, treatment adherence seems to be at best 75% in most studies. Even in symptomatic diseases where lapses in therapy may result in clinically significant symptoms, adherence is still a problem. In glaucoma, the lack of overt symptoms, in theory would tend to decrease the adherence of the patient to pharmacotherapy requiring frequent self-treatment. In tandem studies in glaucoma patients provided with electronic monitors, average adherence (proportion of doses taken) ranged from 65% (pilocarpine 4 times daily) to 73% (timolol twice daily).[14]
In a review of systematic therapy studies in which compliance was evaluated by electronic monitors, the prescribed number of doses per day was inversely related to treatment adherence. Likewise, other studies reported problems with adherence when multiple medications were used. Therefore, it is important to maximize adherence to therapy.[14]

Studies have shown that non-adherent patients are at risk for worsened clinical and economic outcomes.[15] Improving adherence is only a worthwhile goal if, in addition to controlling healthcare costs, adherence improves health and quality of life.[16] One study by Kass and colleagues, estimated average compliance rates of 64% (in eyes with reactive pupils) to 80% (in eyes with non-reactive pupils), a result that is in line with studies using other measures of compliance with glaucoma medications.[17]

Surgical Treatment

When pharmacologic treatment fails to adequately reduce IOP, laser surgery should be considered.[10] The two most common types of laser surgery are argon laser trabeculoplasty (ALT) and selective laser trabeculoplasty (SLT). Both procedures result in an IOP reduction of 20-30%. However, relapse rate is 5-10% of patients per year, for 5- and 10-year success rates of 50% and 32%, respectively,[10] and continued medical therapy is almost always required.[3] Nonetheless, some still consider it as a potential early treatment.[10]

Incisional surgery, the most common being trabeculectomy, should be considered when medical and laser therapies fail.[10] Trabeculectomy is a form of filtering surgery which increases aqueous outflow. Although it is a therapy of last resort, its success rate is very high (80-90% at 5 years).[3]

1.2.5 Alternative Treatment Options (Drug and Non-Drug)

About 5% of glaucoma patients in the U.S. use complementary and alternative medicine to help treat their glaucoma. Commonly used alternative therapies are vitamin supplementation,[18] gingko biloba which increases blood flow to the optic nerve, and cannabis which has a profound but temporary impact on IOP in some patients with non-functional side effects.[18] Although exercise increases blood flow and leads to a chronic reduction of IOP in the normal eye, its effects on glaucomatous eyes are inconclusive.[18]

1.2.6 Place of the Product in Therapy and Expected Outcomes

While Timolol and Brimonidine are commonly prescribed first-line agents to reduce the production of aqueous humor in the eye and increase outflow of aqueous humor via the uveoscleral route, adjunctive or multiple therapies for glaucoma can be problematic in terms of compliance with therapy. Requiring patients to wait a minimum of approximately 5 minutes between the administrations of the individual products may be an even greater burden on the elderly, who comprise the main population taking these medications. Furthermore, decreased compliance may negatively impact the maintenance of therapeutic effect in what can be perceived by the patients as a symptom-free disease. Another concern of the two-bottle adjunctive therapy is the increased exposure to the preservatives that is potentially harmful to the ocular surface.

COMBIGAN™ ophthalmic solution, with the enhanced formulation, may minimize potentially harmful local effects. In a pivotal trial, adverse events related to conjunctival allergy and inflammation were reported significantly less often for patients taking COMBIGAN™ than for patients receiving brimonidine monotherapy, and fewer patients treated with COMBIGAN™ ophthalmic solution discontinued from the study early owing to adverse events. This improvement in tolerability with COMBIGAN™ therapy might be expected because patients receiving brimonidine monotherapy had a dosage of 3 times daily, whereas patients receiving the COMBIGAN™ had a dosage of twice daily and had reduced exposure to brimonidine.[12]

COMBIGAN™ provides the additional IOP reduction that the patient requires with the convenience of a single bottle. Because the dosing regimen is one drop twice daily, the patient administers half the number of eye drops each day as compared with when the medications are administered separately. In addition, having one single bottle reduces the total number of medications. COMBIGAN™ administered twice daily provides an effective and convenient therapeutic alternative for the treatment of glaucoma and ocular hypertension.[12] Given these

benefits, it is anticipated that COMBIGAN™ ophthalmic solution will be used as a second line therapy in the treatment of glaucoma.

2 CLINICAL AND ECONOMIC INFORMATION

2.1 Published and Unpublished Clinical Study Results

2.1.1 Pivotal Safety and Efficacy Trials: COMBIGAN™

Twice-Daily COMBIGAN™ Therapy vs Monotherapy With Timolol or Brimonidine in Patients With Glaucoma or Ocular Hypertension

Objective: To evaluate the intraocular pressure (IOP)–lowering efficacy and safety of COMBIGAN™ ophthalmic solution compared with the brimonidine and timolol medications.

Study Design: Prospective, 12-month, phase 3, randomized, double-masked, parallel-group study comparing COMBIGAN™ twice daily with 0.2% brimonidine 3 times daily or 0.5% timolol twice daily.

Trial Centers: 53 sites throughout the United States.

Study Medication: COMBIGAN™ ophthalmic solution twice daily (n=385), 0.2% brimonidine tartrate 3 times daily (n=382), or 0.5% timolol maleate twice daily (n=392).

Methods: Patients 18 years or older who required bilateral treatment for glaucoma or ocular hypertension were eligible to enroll. Eligible patients had to have a baseline IOP (after washout) between 22 and 34 mm Hg in each eye, with no more than a 5-mm Hg difference between eyes and a best-corrected visual acuity of 20/100 or better OU. Patients received their first dose of medication (1 drop in each eye) after all evaluations at the baseline visit. Thereafter, patients self-instilled 1 drop of the appropriate study medication into both eyes in the morning between 7 and 9 AM, in the afternoon between 1 and 3 PM, and in the evening between 7 and 9 PM. To maintain masking, patients in the COMBIGAN™ group and the timolol group administered study medication in the morning and evening and a vehicle solution in the afternoon. Patients in the brimonidine group administered study medication in the morning, afternoon, and evening. The afternoon dose in all 3 groups (vehicle solution or brimonidine) was provided in a separate, smaller bottle to ensure that all medications were given at the correct time. Follow-up study visits were scheduled at weeks 2 and 6 and at months 3, 6, 9, and 12. The primary efficacy measure was mean change from baseline IOP at each follow-up time point. The safety evaluation included an assessment of reported adverse events, biomicroscopy, tests of visual acuity and visual fields, ophthalmoscopy, cup-disc ratio, heart rate, blood pressure, complete blood cell count, serum chemistry, and urinalysis.

Results: The mean decrease from baseline IOP during 12-month follow up was 4.4 to 7.6 mm Hg with COMBIGAN™ ophthalmic solution, 2.7 to 5.5 mm Hg with brimonidine, and 3.9 to 6.2mm Hg with timolol. Mean IOP reductions were significantly greater with COMBIGAN™ compared with timolol at all measurements ($P \leq .002$) and brimonidine at 8 AM, 10 AM, and 3 PM ($P < .001$) but not at 5 PM. The incidence of treatment related adverse events in the

COMBIGAN™ group was lower than that in the brimonidine group (*P*=.006) but higher than that in the timolol group (*P*<.001). The rate of discontinuation for adverse events was 14.3% with COMBIGAN™, 30.6% with brimonidine, and 5.1% with timolol.

The overall safety profile of COMBIGAN™ ophthalmic solution therapy in this study was consistent with the results of previous studies of the individual components as monotherapies. No safety concerns arose with COMBIGAN™ therapy that had not been observed with the control drugs. Adverse events related to conjunctival allergy and inflammation were reported significantly less often for patients taking COMBIGAN™ than for patients receiving brimonidine monotherapy, and fewer patients treated with the COMBIGAN™ ophthalmic solution discontinued from the study early owing to adverse events.

Conclusion: COMBIGAN™ administered twice daily provides an effective and convenient therapeutic alternative for the treatment of glaucoma and ocular hypertension. COMBIGAN™ twice daily provided greater IOP-lowering efficacy than either 0.5% timolol twice daily or 0.2% brimonidine 3 times daily used as monotherapy. COMBIGAN™ ophthalmic solution was better tolerated than brimonidine monotherapy but less well tolerated than timolol monotherapy.

Sherwood, MB et al: Twice-Daily 0.2% Brimonidine-0.5% Timolol Fixed-Combination Therapy vs Monotherapy With Timolol or Brimonidine in Patients With Glaucoma or Ocular Hypertension. Arch Ophthalmol. 2006;124:1230-1238.[12]

Craven ER et al: 1-Year Comparison of Efficacy and Safety of Brimonidine 0.2%/Timolol 0.5% Fixed Combination vs Brimonidine 0.2% or Timolol 0.5% Monotherapy. Presented at Annual Meeting of the American Academy of Ophthalmology; October 20-23, 2002; Orlando, FL.[19]

Craven ER, Sherwood MB, DuBiner HB: Twelve-Month Randomized Comparison of Fixed-Combination Brimonidine 0.2%/Timolol 0.5% With Each Component as Monotherapy. Presented at the American Academy of Ophthalmology – European Society of Ophthalmology Joint Meeting; October 23-26, 2004; New Orleans, LA.[20]

COMBIGAN™ Therapy Versus Monotherapy: A 3-Month Randomized Trial in Patients with Glaucoma or Ocular Hypertension

Objective: To compare the safety and intraocular pressure (IOP)-lowering efficacy of COMBIGAN™ ophthalmic solution versus each drug used as monotherapy.

Methods: Two prospective, 3-month, randomized, double-masked, parallel-group, phase III trials were conducted at 53 sites throughout the United States. The protocols were identical and the results of the two studies were similar, so the data were pooled to create a larger cohort for the present analysis. The first patient was enrolled in the study on January 14, 2000. All patients had completed 3 months of treatment by April 18, 2001. This study involved patients 18 years of age or older who required bilateral treatment for glaucoma or ocular hypertension. All patients were required to undergo washout of any IOP lowering medications prior to the baseline visit. Washout periods were 4 days for parasympathomimetics and carbonic anhydrase inhibitors, 2 weeks for sympathomimetics and alpha-agonists, and 4 weeks for beta-blockers (alone or in combination), topical prostaglandins, and topical prostamides. Patients had to have a baseline IOP (after washout) between 22 mmHg and 34 mmHg in each eye, with no more than a 5 mmHg difference between eyes, and a best-corrected visual acuity of 20/100 or better in each eye to be eligible for study entry. At the baseline visit, patients were randomly assigned to one of three treatment groups: COMBIGAN™ BID (fixed brimonidine/timolol, COMBIGAN™, Allergan, Inc.; Irvine, CA), timolol 0.5% BID (timolol maleate, Allergan, Inc.; Irvine, CA), or brimonidine 0.2% TID (ALPHAGAN®, Allergan, Inc.; Irvine, CA), using a 1:1:1 allocation in blocks of 6. The randomization sequence was generated by the study sponsor using the PLAN procedure in SAS version 6.12 (SAS Institute Inc., Cary, NC). In order to maintain masking, patients in the COMBIGAN™ group and the timolol group administered study medication in the morning and evening and a vehicle solution in the afternoon. Patients in the brimonidine group administered study medication in the morning, afternoon, and evening. The afternoon dose in all three groups (vehicle solution or brimonidine) was provided in a separate, smaller bottle to ensure that all drugs were given at the correct time. Patients received their first dose of medication after all evaluations at the baseline visit. Thereafter, patients self-instilled the study medication in the morning between 7 AM and 9 AM, in the afternoon between 1 PM and 3 PM, and in the evening between 7 PM and 9 PM. Follow-up study visits were scheduled at weeks 2 and 6, and month 3.

Results: In all, 1159 patients were randomized to treatment: 385 in the COMBIGAN™ group, 382 in the brimonidine group and 392 in the timolol group. A total of 999 patients (86.2%) completed 3 months of assigned therapy. Of the 160 patients (13.8%) who discontinued participation, 31 (2.7%) did so because of uncontrolled IOP, 81 (7.0%) because of adverse events, and 48 (4.1%) owing to other reasons. The mean decrease in IOP from baseline was significantly greater in the COMBIGAN™ group than in the timolol group at all measurements on all follow-up visits throughout the study ($P \leq 0.008$ at 8 AM, 10 AM, and 3 PM; $P \leq 0.026$ at 5 PM). The mean decrease in IOP from baseline was significantly greater in the COMBIGAN group than the brimonidine group at all 8 AM, 10 AM, and 3 PM follow-up measurements throughout the study ($P < 0.001$) but not at the 5 PM measurements. Mean IOP was significantly lower in the COMBIGAN™ group than in either of the monotherapy groups at all measurements on all follow-up visits except for the 5 PM

measurement at week 2 ($P< 0.001$ at 8 AM, 10 AM, and 3 PM; $P\leq 0.018$ at 5 PM). At this time point, mean IOP was lower in the COMBIGAN™ group than in the timolol group ($P< 0.001$), while the difference from the brimonidine group tended toward significance ($P= 0.093$). A significantly greater percentage of patients in the COMBIGAN group than in either monotherapy group maintained mean diurnal IOP (IOP averaged over all measurements on a given visit) of less than 18 mmHg through out the 3-month study ($P< 0.001$). Mean diurnal IOP was below this level in 56% of patients in the COMBIGAN™ group, 27% of patients in the brimonidine group, and 37% of patients in the timolol group.

Safety results: Of the 1159 patients enrolled in this study, 999 (86%) completed 3 months of dosing. Nearly half of the patients who discontinued from the study did so owing to adverse events (81 of 160). The rate of discontinuations resulting from adverse events was similar in the COMBIGAN™ group and the timolol group (3.6% in each group, $P= 0.961$) and higher in the brimonidine 0.2% TID group (13.9%, $P< 0.001$ versus COMBIGAN™ ophthalmic solution). The overall incidence of adverse events in the COMBIGAN™ BID group (211 of 385, 54.8%) was similar to the incidence in the timolol BID group (205 of 392, 52.3%; $P= 0.483$) and lower than the incidence in the brimonidine TID group (245/382, 64.1%; $P= 0.008$). The most common adverse events that showed significant differences between treatment groups were ocular burning and stinging. Ocular burning and stinging occurred more often in the COMBIGAN™ group than in the brimonidine group, at rates comparable to those in the timolol group.

Conclusion: COMBIGAN™ ophthalmic solution therapy resulted in significantly greater reductions in IOP than either component used as monotherapy. Significantly more COMBIGAN™ therapy patients than monotherapy patients achieved clinically significant endpoints of greater than 20% reductions in IOP and target pressures of less than 18 mmHg. The safety profile of COMBIGAN™ was favorable with no evidence for a potentiation of adverse events.

Craven ER et al: Brimonidine and Timolol Fixed-Combination Therapy Versus Monotherapy: A 3-Month Randomized Trial in Patients with Glaucoma or Ocular Hypertension. Journal of Ocular Pharmacology and Therapeutics 2005;21(4):337-348.[21]

Craven ER for the Alphagan®/Timolol Study Groups I and II: A 3-Month Comparison of the Efficacy and Safety of Brimonidine Tartrate 0.2%/Timolol 0.5% Fixed Combination (BID) With Timolol 0.5% (BID) and Brimoonidine 0.2% (TID) Monotherapies. Presented at the 29th International Congress of Ophthalmology; April 21-25, 2002; Sydney, NSW, Australia.[22]

Craven ER for the Alphagan®/Timolol Study Groups I and II: A 3-Month Comparison of the Efficacy and Safety of Brimonidine Tartrate 0.2%/Timolol 0.5% Fixed Combination (BID) With Timolol 0.5% (BID) and Brimoonidine 0.2% (TID) Monotherapies. Presented at the Annual Meeting of the Association for Research in Vision and Ophthalmology; May 5-10, 2002; Fort Lauderdale, FL.[23]

2.1.2 Supportive Safety and Efficacy Trials: COMBIGAN™

COMBIGAN™ as safe and effective as adjunctive therapy in glaucoma / OHT

Objectives: The purpose of this study was to compare the safety and efficacy of COMBIGAN™ ophthalmic solution with the 2 timolol and brimonidine agents used adjunctively (hereafter referred to as Adjunctive).

Methods: Three-month, multinational, randomized, double-masked, parallel-group.
*Outcome Measures***:** IOP was measured at hour 0 (09:30 ± 1 hr) and hour 2. Safety measures comprised adverse events, vital signs, biomicroscopy, ophthalmoscopy, visual acuity, visual fields and laboratory evaluations. Analysis of IOP used data from the worse eye (eye with the higher IOP at baseline) or the right eye if equal IOP values. Additional sub-group analysis of that population which used beta-blocker as run-in monotherapy. Non-inferiority was established when the upper limit of the 95% confidence interval on the between-group difference in mean change from baseline in IOP fell below 1.5 mmHg.

Results: *Efficacy:* Both the COMBIGAN™ ophthalmic solution and adjunctive treatments had statistically and clinically significantly lowered IOP from baseline at each follow-up timepoint at each visit ($p < 0.001$). Mean decrease from monotherapy baseline IOP ranged from 4.4 mm Hg to 4.9 mm Hg at trough (hour 0) in both groups. The mean change from baseline in IOP and mean IOP values of the Combination group were non-inferior to those achieved by the Adjunctive group in the ITT with LOCF population at all time-points. For the between-group differences, the upper limits of the 95% confidence interval also fell below 1.0 mm Hg at all time-points and all visits.

Safety: Both COMBIGAN™ and adjunctive treatments were safe and well-tolerated. Overall treatment-related AE incidence was low with no statistically significant difference between groups. Of these, the most common were ocular pain, ocular pruritus and headache. All events reported already known from the profiles of each of the agents used alone or adjunctively. No treatment-related bradycardia or hypotension reports. Most AEs were mild to moderate in severity and led to few discontinuations. No clinically significant changes from baseline with no statistically significant between-group differences for: all laboratory haematological, biochemical and urological assessments and vital sign measurements. visual acuity, visual fields and cup:disc ratio. Overall the fixed combination was effective, safe and well-tolerated.

Conclusions: Robust evidence is provided that the IOP-lowering effect of COMBIGAN™ ophthalmic solution is consistently non-inferior to that achieved by adjunctive use of the individual agents. The safety profile between both groups is comparable, no unexpected treatment-related adverse events were seen. It is anticipated that the simplified dosage regimen will have a positive effect on compliance. Thus, adjunctive therapy can be replaced with COMBIGAN™ with confidence.

Goni FJ, Bossowska IJ, Ingram AM for the Brimonidine/Timolol Study Group: New Brimonidine/Timolol fixed combination as safe and effective as adjunctive therapy in glaucoma/OHT. Presented at European Glaucoma Society Meeting (EGS); May 30-June 03, 2004; Florence, Italy[24]

Efficacy and Safety of the IOP-Lowering COMBIGAN™

Objective: To evaluate the safety and efficacy of COMBIGAN™ in patients with glaucoma or ocular hypertension. Studies were conducted to compare twice-daily COMBIGAN™ ophthalmic solution to 1) monotherapy with brimonidine 0.2% TID or timolol 0.5% BID and 2) concomitant therapy with brimonidine 0.2% BID and timolol 0.5% BID.

Methods: COMBIGAN™ *versus monotherapy*: Two identical, 12-month, randomized, double-masked, multicenter, parallel-group, clinical trials were conducted. Data from the 2 trials were pooled for analysis. Patients with glaucoma or ocular hypertension were randomized to treatment with COMBIGAN™ BID, brimonidine 0.2% TID, or timolol 0.5% BID. IOP was measured at 8 am (prior to dosing), 10 am, 3 pm (prior to dosing), and 5 pm at baseline, weeks 2 and 6, and months 3, 6, and 12. At month 9, IOP was measured at 8 am and 10 am. The 5 pm IOP measurement, at peak effect after the afternoon dose in the brimonidine TID group, was included to determine whether the added dose of brimonidine in the afternoon provided additional IOP lowering compared with COMBIGAN™ ophthalmic solution, which was dosed twice daily. IOP measurements from both eyes of an individual patient were averaged and used in the analyses.

COMBIGAN™ *versus concomitant therapy*: 12-week, randomized, multicenter, double-masked, parallel-group, noninferiority study. Patients with inadequate IOP control (IOP from 22-34 mm Hg) after at least 3 weeks of run-in on any monotherapy were switched to treatment with COMBIGAN™ BID or concomitant brimonidine 0.2% BID and timolol 0.5% BID. IOP was measured at baseline and weeks 2, 6, and 12 at hour 0 (approximately 9:30 am, prior to dosing) and hour 2. Efficacy analyses used IOP in the worse eye (eye with higher IOP at baseline, hour 0) and a strategy of combined tests of noninferiority and superiority. COMBIGAN™ ophthalmic solution was determined to be noninferior to concomitant brimonidine and timolol when the upper limit of the 95% confidence interval (CI) for the difference in mean change from baseline IOP (COMBIGAN™ minus concomitant) was < 1.5 mm Hg.

Results: COMBIGAN™ *ophthalmic solution versus monotherapy*: Baseline mean IOP at 8 am, 10 am, and 3 pm was similar between treatment groups. Baseline mean IOP at 5 pm was slightly lower in the COMBIGAN™ group than in the timolol group ($P = .010$) or brimonidine group ($P = .058$), but was within 0.6 mm Hg. Mean IOP at the 22 measurements over all follow-up visits ranged from 15.7 to 18.7 mm Hg with COMBIGAN™, 17.2 to 21.6 mm Hg with brimonidine, and 17.9 to 19.6 mm Hg with timolol. Mean IOP was significantly lower with COMBIGAN™ ophthalmic solution compared with timolol at all follow-up measurements ($P \leq .002$) and compared with brimonidine at all 8 am, 10 am, and 3 pm measurements ($P < .001$). The 5 pm measurements were 2 hours after the last dose of brimonidine and 9 hours after the last dose of the COMBIGAN™. The only significant difference between the COMBIGAN™ and brimonidine groups at 5 pm was at week 6 when mean IOP was significantly lower in the COMBIGAN™ group than in the brimonidine group ($P = .044$). The distribution of patients with a mean follow-up IOP (average of IOP from all 22 follow-up timepoints) within specified target pressure ranges (< 14 mm Hg, 14-17.5 mm Hg, and > 17.5 mm Hg) favored the COMBIGAN™ group over each of the monotherapy groups. There was a significant shift toward the lower target pressure ranges in the COMBIGAN™ group compared with the monotherapy groups ($P < .001$). The incidence of treatment-related adverse events in the

COMBIGAN™ group (53.0%) was higher than in the timolol group (40.8%, $P < .001$) but lower than in the brimonidine group (62.8%, $P = .006$). The incidence of treatment-related adverse events of the conjunctiva was lower in the COMBIGAN™ ophthalmic solution BID group than in the brimonidine TID group (26.0% vs 39.8%, $P < .001$). The incidence of allergic conjunctivitis was 5.2% in the COMBIGAN™ BID group compared with 9.4% in the brimonidine 0.2% TID group ($P < .024$).

COMBIGAN™ versus concomitant therapy: The mean reduction from baseline IOP was similar between the COMBIGAN™ ophthalmic solution and concomitant therapy groups at all timepoints during follow-up and ranged from 4.4 to 5.3 mm Hg in each group. The mean changes from baseline IOP within each treatment group were clinically and statistically significant ($P < .001$) at all timepoints. At week 12, the mean change from baseline IOP at hour 0 (the primary efficacy endpoint) was -4.9 mm Hg for both groups, and the upper limit of the 95% CI for the difference between groups (COMBIGAN™ minus concomitant) was 0.79, demonstrating noninferiority of the COMBIGAN™ to concomitant therapy. Over follow-up, differences between groups (COMBIGAN™ minus concomitant) ranged from -0.30 to 0.14 mm Hg, and none were statistically significant ($P \geq .345$). COMBIGAN™ ophthalmic solution was noninferior to concomitant therapy: the upper limit of the 95% CI of the difference (COMBIGAN™ minus concomitant) was ≤ 0.83 mm Hg at all timepoints during follow-up. Mean IOP was similar between the 2 treatment groups at all timepoints in the study. Mean IOP at follow-up measurements ranged from 17.3 to 20.6 mm Hg in the COMBIGAN™ group minus 17.1 to 20.5 mm Hg in the concomitant group. Differences between groups (COMBIGAN™ and concomitant) ranged from -0.05 to 0.35 mm Hg, and none were statistically significant ($P \geq .274$). COMBIGAN™ was noninferior to concomitant therapy: the upper limit of the 95% CI of the difference (COMBIGAN™ ophthalmic solution minus concomitant) was ≤ 0.97 mm Hg at all timepoints and visits.

Safety and tolerability evaluations of COMBIGAN™ were favorable. No unexpected adverse events were associated with COMBIGAN™ treatment.

Conclusion: COMBIGAN™ ophthalmic solution therapy is an effective and convenient therapeutic alternative for the treatment of glaucoma and ocular hypertension. COMBIGAN™ BID therapy provides sustained IOP lowering equivalent to concomitant therapy with the individual components and superior to either brimonidine TID or timolol BID monotherapy. COMBIGAN™ is clinically superior to brimonidine 0.2% TID in long-term safety. Ocular allergy is less common with COMBIGAN™ than with brimonidine 0.2% TID.

Goni FJ, Craven ER, Chou C: Efficacy and Safety of the IOP-Lowering Fixed Combination Brimonidine 0.2%/Timolol 0.5%. Presented at 2006 International (World) Congress of Ophthalmology (WOC); February 19-24, 2006; São Paulo, Brazil[25]

Randomized, Parallel Comparison of the Efficacy and Tolerability of Twice-Daily 0.2% Brimonidine/0.5% Timolol (COMBIGAN™) vs. 2.0% Dorzolamide/0.5% Timolol (Cosopt®) Fixed Combination Therapies in Patients with Glaucoma or Ocular Hypertension

Objective: To determine the efficacy and tolerability of COMBIGAN™ vs. 2.0% dorzolamide/0.5% timolol (*Cosopt®*) in patients with glaucoma or ocular hypertension.

Methods: Pooled data from two investigator-masked, randomized, 3 month-parallel comparison studies performed at 10 sites with identical protocols. Patients with open angle glaucoma or ocular hypertension requiring additional IOP lowering were washed out from all topical glaucoma medications except prostaglandin analogs (PG). Patients were divided into monotherapy (N=101) and PG adjunctive (N=79) groups. Patients in the monotherapy group were randomized to receive either COMBIGAN™ ophthalmic solution or *Cosopt*® twice daily and those in the adjunctive group were randomized to receive either COMBIGAN™ or *Cosopt*® twice daily in addition to their topical PG. Patient rated stinging, burning, and unusual taste on a questionnaire. Ocular allergy was not measured.

Results: There were no statistical differences in baseline IOPs between COMBIGAN™ ophthalmic solution and *Cosopt*® treated eyes in either the monotherapy (23.0 and 23.6 mm Hg, P=0.522) or the PG adjunctive groups (21.9 and 21.0 mm Hg, P=0.277). After 3 months, the mean IOP was 15.6 mm Hg for COMBIGAN™ and 17.2 mm Hg for *Cosopt*® treated eyes (P=0.031) as monotherapy, and 15.3 mm Hg for COMBIGAN™ and 16.1 mm Hg for *Cosopt*® (P = 0.391) treated eyes as adjunctive to a PG. The mean decrease from baseline was 7.7 mm Hg (32.3%) for COMBIGAN™ and 6.7 mm Hg (26.1%) for *Cosopt*® (P=0.040) as monotherapy and 6.9 mm Hg (29.3%) for COMBIGAN™ and 5.2 mm Hg (23.5%) for *Cosopt*® (P=0.213) adjunctive to a PG. Patients treated with COMBIGAN™ ophthalmic solution reported significantly less moderate to severe stinging (P<0.0001), burning (P<0.0149), and unusual taste (P<0.0047) than patients treated with *Cosopt*®.

Conclusion: In this pooled data set, COMBIGAN™ provides at least comparable or greater IOP lowering than *Cosopt*®. COMBIGAN™ ophthalmic solution appears to have a better tolerability profile than *Cosopt*®.

Nixon DR, Hollander DA. Randomized, Parallel Comparison of the Efficacy and Tolerability of Twice-Daily 0.2% Brimonidine/0.5% Timolol (COMBIGAN®) vs. 2.0% Dorzolamide/0.5% Timolol (Cosopt®) Fixed Combination Therapies in Patients with Glaucoma or Ocular Hypertension.. American Academy of Ophthalmology; Nov 10-13, 2007; New Orleans, LA.[26]

COMBIGAN™ Therapy in Glaucoma Management

Objective: The COMBIGAN™ Early Experience Data trial was undertaken to obtain data in a real-life, clinical setting about the efficacy, tolerability, and safety of COMBIGAN™ The two primary outcome measures were mean IOP and patient satisfaction (to evaluate patients' experience with COMBIGAN™ secondary outcome measures included adverse events and physician satisfaction (to evaluate physicians' experience with COMBIGAN™ ophthalmic solution).

Methods: The COMBIGAN™ Early Experience Data trial was an open-label, prospective, two month surveillance study, with individual investigators selecting who would be included in the trial. The open-label study design, where both the provider and the patient are aware of the treatment being given, may bias the results. The final number of patients enrolled in the trial was 453, and those patients were followed and evaluated at 47 centers across Canada. To be included in the trial, patients had to either require further IOP lowering from what they were already achieving, or they stood to benefit from both the greater convenience and compliance of fixed-combination therapy.

The baseline visit included just the one measurement, therefore diurnal fluctuation presents a possible limitation in that it was not accounted for in this study; however, to minimize the variance in fluctuation throughout the study, investigators were instructed to schedule Visits 2 and 3 within ± 1 hour of the time of the baseline visit. At baseline, 51% of the study patients were receiving monotherapy, and 49% were on a multi-therapy regimen.

Medications that were being taken by study patients at baseline included Xalatan®, Timoptic®, ALPHAGAN®, *Cosopt®,* and LUMIGAN®; some patients were also taking *Travatan®,* but they were fewer in number. Patients could be on one or more of these medications at baseline. COMBIGAN™ ophthalmic solution therapy was initiated as monotherapy in 47.7% of study patients, while the remainder (52.3%) received COMBIGAN™ as add-on therapy. When used adjunctively, COMBIGAN™ was most frequently used in combination with a hypotensive lipid.

Results: In terms of overall results, the COMBIGAN™ Early Experience Data trial demonstrated that COMBIGAN™ ophthalmic solution (used concomitantly with other medications or as monotherapy) provided an additional 3.8 mm Hg reduction in mean IOP, bringing most patient eyes to target. Furthermore, 68% of the COMBIGAN™ treated eyes attained an additional ≥15% IOP reduction from baseline. By study endpoint, target IOP of ≤18 mm Hg was achieved by 70% of eyes treated with COMBIGAN™ (in contrast to 31% at baseline).

In looking at patients switched from *Cosopt*® to COMBIGAN™ (whether as monotherapy or adjunctive therapy), it was noted that COMBIGAN™ ophthalmic solution further reduced mean IOP beyond what *Cosopt*® had thus far been able to achieve. COMBIGAN™ provided an additional 2.7 mm Hg (or 12%) mean IOP reduction, and 45% of all eyes had an additional >15% IOP decrease. It was also interesting to note that the number of treated eyes that achieved the ≤18 mm Hg target IOP more than doubled (from 29% to 64%) once patients were switched to COMBIGAN™ adjunctive therapy from *Cosopt*® adjunctive therapy.

Similarly favorable results were demonstrated among patients who were switched from *Cosopt*® monotherapy to COMBIGAN™ monotherapy. COMBIGAN™ treated eyes benefited from an additional >14% reduction (or -3.3 mm Hg) in mean IOP. However, perhaps the most compelling result was the increase in the percentage of patient eyes that achieved target IOP (≤18 mm Hg) once switched from *Cosopt*® to COMBIGAN™ ophthalmic solution (monotherapy): the percentage that achieved target went from the baseline of 12.8% to 56.8% by study endpoint.

When taken as either monotherapy or adjunctive therapy (n= 80, monotherapy n= 25), the overwhelming majority of patients rated COMBIGAN™ as superior to *Cosopt*®. On measures of patient satisfaction, convenience, and ocular comfort, 80%, 88%, and 92% of respondents preferred COMBIGAN™ ophthalmic solution over *Cosopt*® in those respective measures. Patient satisfaction is crucial in ensuring their compliance to a glaucoma therapy regimen; the more likely a patient is to comply with his/her dosing regimen, the more likely treatment will be used to its maximal therapeutic ability. COMBIGAN™ also rated highly in terms of physician satisfaction, with 100% of physicians (n=47) stating that they would prescribe it for their patients, citing ease of use, convenience, decreased cost compared to *Cosopt*®, and superior patient compliance as their top reasons for their overwhelming approval. Furthermore, coverage of COMBIGAN™ on provincial drug plans such as the Ontario Drug Benefit Plan (ODB) and Quebec's RAMQ has increased its cost-effectiveness and accessibility.

Conclusion: Fixed-combination agents offer benefits such as decreased preservative, convenience, help with compliance, improved cost, and safety. COMBIGAN™ ophthalmic solution was effective and comfortable and should be considered in patients who would potentially benefit from its effectiveness and patient tolerability as well as those who would prefer the convenience of a single-bottle solution — thereby improving ease of use, as well as patient compliance.

Crichton ACS: Timolol/Brimonidine Combination Therapy in Glaucoma Management. Clinical & Surgical Journal of Ophthalmology 2005;23(10):356-359.[27]

CEED II: An In-Depth Look at the Latest Findings

Background: There are numerous benefits of combination agents for IOP reduction: decreased toxicity, simplified dosing schedules, and increased patient comfort. All of these measures lead to improved patient compliance. Phase III studies of COMBIGAN™ ophthalmic solution demonstrated the efficacy and safety of the product over 12 months of treatment. The CEED trials were subsequently initiated to determine the real-life efficacy, tolerability and safety of COMBIGAN™ as measured by IOP and patient satisfaction.

Objective: Summarize the results of CEED I and II. CEED II was undertaken to advance what was learned from CEED I, with additional objectives in mind: to see if similar trends would exist with larger populations.

CEED I
Methods: open-label, prospective, two-month surveillance study that enrolled 453 patients at 47 centres across Canada.

Results: When comparing COMBIGAN™, vs. *Cosopt®,* treated eyes achieving target pressures of ≤18mmHg more than doubled (29% to 64%) and 45% of all eyes achieved additional IOP reductions of ≥15%. The majority of patients felt COMBIGAN™ ophthalmic solution was superior in all satisfaction assessments. In a subanalysis of patients switched from Cosopt® to COMBIGAN™ monotherapy, 80% of patients were more satisfied with COMBIGAN™ than *Cosopt®.*

CEED II
Methods: Openlabel, prospective, two-month surveillance trial that enrolled 2,133 patients at 123 centres across Canada. Combigan® was given as either replacement therapy or adjunctive therapy, with study visits at baseline, one month (Visit 2), and two months (Visit 3) for evaluation.

Results: COMBIGAN™ demonstrated a total IOP reduction of 17.8% from baseline. The overall IOP percent change from baseline resulting from COMBIGAN™ therapy resulted in 42% of the treated eyes achieving ≥15% reduction in IOP from baseline. Upon switching (from *Cosopt®* to COMBIGAN™), COMBIGAN™ ophthalmic solution provided an additional IOP reduction of 10.8%.

The trial demonstrated that COMBIGAN™ provided a statistically significant reduction in mean IOP. In addition, physicians were unanimous in rating COMBIGAN™ very high in ease of use, convenience and decrease cost compared to *Cosopt®.* The CEED II study not only solidified the robust efficacy of COMBIGAN™ ophthalmic solution over *Cosopt®* in both the adjunctive and monotherapy settings, but also established the high level of tolerability of the product in a large, real-world population.

Conclusions: COMBIGAN™ is a safe, well-tolerated and effective treatment that should be considered in patients who would benefit from an easy to use and convenient therapy.

Ahmed, I. CEED II: An In-Depth Look at the Latest Findings. Clinical & Surgical Journal of Ophthalmology 25:1, 2007[28]

Fixed Combination Brimonidine–Timolol (COMBIGAN™) versus Fixed Combination Dorzolamide–Timolol (Cosopt®) Each Given Twice Daily to Reduce Intraocular Pressure in Subjects With Open Angle Glaucoma or Ocular Hypertension

Objectives: To evaluate the efficacy of fixed combination brimonidine–timolol (COMBIGAN™) versus fixed combination dorzolamide–timolol (*Cosopt®*) given twice daily in patients with either primary open angle glaucoma or ocular hypertension.

Methods: 30 subjects were enrolled in this prospective, multicenter, masked–observer, crossover comparison study. After a wash out period, patients were randomized to COMBIGAN™ ophthalmic solution or *Cosopt®* for the first 4–week treatment period. Subjects then were washed for 4 weeks and started on the opposite medication for the second 4–week period. Intraocular pressure (IOP) was measured at 8:00 am, 12:00 pm, and 4:00 pm at each baseline and at the end of each treatment period. Unsolicited ocular adverse events were also recorded.

Results: The baseline mean diurnal IOP for all 30 subjects (30 eyes) was 22.9 ± 1.6 mmHg. Both fixed combinations significantly reduced IOP compared with baseline ($p<0.00001$). The mean diurnal IOP following 4 weeks of therapy was 15.0 ± 2.1 mmHg for COMBIGAN™ ophthalmic solution and 15.4 ± 2.1 mmHg for *Cosopt®* ($p=0.510$). The mean diurnal IOP reduction was (7.8 ± 1.9 mmHg for COMBIGAN™ and 7.4 ± 1.8 mmHg for *Cosopt®* ($p=0.430$). Overall, 14 subjects complained about ocular adverse events: 2 for COMBIGAN™ ophthalmic solution, 7 for *Cosopt®* and 5 for both drugs. Although there was no significant difference between the number of subjects that reported ocular adverse events with COMBIGAN™ (n=7) and Cosopt® (n=12) ($p=0.359$), *Cosopt®* caused more ocular stinging upon instillation (n=9) than COMBIGAN™ (n=1) ($p=0.027$).

Conclusions: This study suggests that COMBIGAN™ and *Cosopt®,* each given twice daily, have similar efficacy in primary open angle glaucoma or ocular hypertensive subjects.

Arcieri ES, Arcieri RS, Pereira AC, Andreo EG, Finotti IG, Sa Filho WF. Comparing the fixed combination brimonidine-timolol versus fixed combination dorzolamide-timolol in patients with elevated intraocular pressure. Curr Med Res Opin. 2007;23(4):683-9.[29]

Arcieri, E.S. Pereira, A.C. A., Andreo, E.G. V., Finotti, I.G. A., Arcieri, R.S., Sá Filh, W.F. Fixed Combination Brimonidine–Timolol (COMBIGAN®) versus Fixed Combination Dorzolamide–Timolol (Cosopt®) Each Given Twice Daily to Reduce Intraocular Pressure in Subjects With Open Angle Glaucoma or Ocular Hypertension. Invest Ophthalmol Vis Sci 2006;47: E-Abstract 434.[30]

Ocular Comfort of COMBIGAN® (Brimonidine 0.2% and Timolol 0.5%) Versus Cosopt® (Dorzolamide 2% and Timolol 0.5%)

Purpose: Compliance with medication is fundamental to the success of self administered therapy and is especially critical in chronic, slowly progressive, asymptomatic diseases such as glaucoma. Many factors contribute to patient compliance including convenience and comfort. To improve patient convenience, fixed combinations of 2 ocular hypotensive agents [COMBIGAN™ and *Cosopt*® (dorzolamide/timolol) have been developed. Studies suggest, however, that there may be differences in the comfort of these fixed-combination products. The purpose of this study was to compare the ocular comfort of COMBIGAN™ ophthalmic solution and *Cosopt*®.

Methods: Single-centre, randomized, double-masked, paired comparison of the ocular comfort of a single dose of 2 different ophthalmic medications. Thirty normal subjects were randomized to receive COMBIGAN™ in one eye and *Cosopt*® in the fellow eye. Ocular discomfort was graded on a 6-point Ocular Discomfort Scale (ODS) where 0 = normal, no discomfort and 5 = definite, unbearable discomfort. All subjects had to have a score of 0 prior to drop instillation. The ODS was completed at 30 to 40 seconds and at 5 to 6 minutes after instillation of each ophthalmic medication. Data were analyzed with nonparametric tests.

Results: COMBIGAN™ ophthalmic solution was significantly more comfortable than *Cosopt*® ($P < .0001$) at the 30- to 40-second evaluation. At 30 to 40 seconds, 24 (80%) patients found COMBIGAN™ to be more comfortable than *Cosopt*®. Five minutes after administration, there was no difference in ocular discomfort between treatments ($P = .129$). The relationship between the number of patients who found COMBIGAN™ to be the more comfortable treatment and the time elapsed after eyedrop instillation was significant ($P < .0001$ Fisher exact test). There were no adverse events.

Conclusion: COMBIGAN™ was more comfortable than *Cosopt*® upon instillation. This is likely to be an important factor in determining patient compliance with these medications.

Chan K, Testa M, McCluskey P. Ocular comfort of COMBIGAN (brimonidine 0.2% and timolol 0.5%) versus Cosopt (dorzolamide 2% and timolol 0.5%). Poster presented at: 6th International Glaucoma Symposium; March 28-31, 2007; Athens, Greece. [31]

Fixed Combination Timolol/Dorzolamide versus Timolol/Brimonidine: A Randomized Clinical Trial

Objectives: A prospective randomized controlled trial comparing fixed combination timolol 0.5%/dorzolamide 2% with timolol 0.5%/brimonidine 0.2% to determine which combination preparation provides superior intraocular pressure (IOP) control and a better side-effect profile.

Methods: Patients with any type of glaucoma using timolol/dorzolamide were identified from the Moorfields Eye Hospital pharmacy database and review of clinic notes. Those with stable IOP of ≤22mmHg using timolol/dorzolamide alone or with other medications were invited to take part in a prospective, randomized trial and allocated timolol/dorzolamide or timolol/brimonidine in a double masked fashion. Randomization was by patient according to a computer generated list held by the dispensing pharmacist. Where both eyes were eligible the right eye was selected for analysis. Primary variable was IOP measured at baseline, four weeks and 12 weeks. Secondary variables included side-effects and patient preference.

Results: 1400 patients were screened of whom 825 were eligible for enrolment. 54 patients have completed the trial; 42 were male, mean age [range] was 69 years [26-87]. Of the 26 eyes randomized to timolol/dorzolamide mean IOP was 15.2mmHg [9-20] at baseline, 15.5 mmHg [12-21] at four weeks and 17.8mmHg [14-22] at twelve weeks. Of 28 eyes randomized to timolol/brimonidine mean IOP was 15.5mmHg [11-22] at baseline, 15.0mmHg [10-19] at four weeks and 15.7mmHg [12-23] at twelve weeks. Three patients developed a "red eye", exited the trial and were unmasked. Two were using timolol/dorzolamide and one timolol/brimonidine.

Conclusions: Both fixed combinations had a comparable effect on IOP and a low incidence of side-effects.

Spratt, A. Ogunbowale, L. Franks, W. Fixed combination timolol/dorzolamide versus timolol/brimonidine: a randomized clinical trial. Invest Ophthalmol Vis Sci. 2007; 48: E-Abstract 4822.[32]

2.2 Other Studies

Dorzolamide/Timolol Fixed Combination Versus Concomitant Administration of Brimonidine and Timolol in Patients with Elevated Intraocular Pressure: A 3-Month comparison of Efficacy, Tolerability, and Patient-Reported Measures

Objective: To compare the intraocular pressure (IOP) lowering effect, tolerability, and patient-reported measures of the dorzolamide/timolol fixed combination and the concomitant administration of brimonidine and timolol after 3 months.

Methods: Four hundred ninety-two patients with ocular hypertension, primary open-angle glaucoma, exfoliative glaucoma, or pigmentary glaucoma participated in this randomized, observer-masked, multicenter study. Following 3 weeks of timolol monotherapy, patients with a peak IOP of $\geq$22 mm Hg were randomized to receive either fixed combination dorzolamide/timolol twice daily or concomitant brimonidine plus timolol twice daily for 3 months. The IOP lowering effects at peak and trough, tolerability, and patient-reported convenience and satisfaction were measured at months 1 and 3.

Results: A total of 492 patients were randomized at 45 study sites. Of these, 242 patients were randomized to dorzolamide/timolol and 250 patients were randomized to brimonidine plus timolol. Four hundred forty-six (91%) patients completed the study and 46 (9%) patients discontinued from the study. At month 3 peak, the dorzolamide/timolol group had an adjusted mean (SE) change from baseline IOP of −4.30 (0.24)mmHg versus −5.27 (0.23) mm Hg in the brimonidine-plus-timolol group, with a treatment difference of 0.97 mm Hg (95% CI: 0.40, 1.53). At the month 3 trough time point and both month 1 timepoints, the 95% CIs of the treatment differences were within the prespecified comparability boundary of ±1.5 mm Hg. The incidence of drug-related adverse experiences was similar between treatment groups. Throughout the study, patients were monitored for signs and symptoms of adverse experiences. During the 3-month active treatment period, 112 patients (46%) in the dorzolamide/timolol group and 111 patients (45%) in the brimonidine-plus-timolol group reported at least 1 adverse experience. Sixty-eight patients (28%) in the dorzolamide/timolol group and 53 patients (21%) in the brimonidine-plus-timolol group reported systemic or ocular adverse experiences that were considered drug related. Discontinuation from the study due to a drug-related adverse experience occurred for 9 patients (4%) in the dorzolamide/timolol group and 14 patients (6%) in the brimonidine-plus-timolol group. Patient reported assessments of convenience and satisfaction showed no statistically significant differences between treatment groups.

Conclusion: The IOP-lowering effect of the dorzolamide/timolol fixed combination and concomitant brimonidine plus timolol were comparable at 3 of the 4 time points measured. Patient-reported measures and the incidence of adverse experiences in both treatment groups were similar.

Solish AM et al: Dorzolamide/Timolol Fixed Combination Versus Concomitant Administration of Brimonidine and Timolol in Patients with Elevated Intraocular Pressure: A 3-Month Comparison of Efficacy, Tolerability, and Patient-Reported Measures. J Glaucoma 2004;13:149-157.[33]

Dorzolamide/Timolol Combination Versus Concomitant Administration of Brimonidine and Timolol: Six-Month Comparison of Efficacy and Tolerability

Objective: To compare the efficacy and tolerability of the 2% dorzolamide/0.5% timolol combination ophthalmic solution twice daily to the concomitant administration of 0.2% brimonidine ophthalmic solution twice daily and 0.5% timolol ophthalmic solution twice daily.

Methods: Randomized, multicenter, observer-masked, parallel-group study. Two hundred ninety-three patients with ocular hypertension or primary open-angle glaucoma participated. After an open-label 3-week 0.5%timolol run-in period, patients with an hour 2 intraocular pressure (IOP) of $\geq$ 22 mmHg were randomly assigned to receive either the dorzolamide/timolol combination twice daily or the concomitant use of brimonidine twice daily and timolol twice daily (brimonidine + timolol) for 6 months.

The IOP-lowering effects at hour 0 and hour 2 were collected at 1, 3, and 6 months. It was hypothesized that both treatment regimens would have comparable hour 2 IOP-lowering effects at month 3. The treatments were considered comparable if the two-sided 95% confidence interval of the treatment difference was within $\pm$ 1.5 mmHg. Tolerability data were also collected at 1, 3, and 6 months.

Results: The primary efficacy analysis was based on the modified intent-to-treat population. At month 3, hour 2, the dorzolamide/timolol group had an adjusted mean (standard error) change in IOP of -5.04 (0.30) mmHg versus -5.41 (0.30) mmHg in the brimonidine + timolol group, with a treatment difference of 0.36 (0.40) mmHg (95% confidence interval [CI] of -0.42–1.14 mmHg).

At month 3, hour 0, the dorzolamide/timolol group had a change in IOP of -3.66 (0.29) mmHg versus -4.15 (0.28) mmHg in the brimonidine + timolol group, with a treatment difference of 0.49 (0.39) mmHg (95% CI of -0.27–1.25 mmHg). Likewise, at all other observed time points, the 95% confidence interval of the treatment difference was within $\pm$ 1.5 mmHg.

Ninety-three patients (64%) in the dorzolamide/timolol group and 88 patients (60%) in the brimonidine + timolol group had adverse experiences that were deemed drug related by the investigator, for which 7 patients (5%) in the dorzolamide/timolol group and 8 patients (5%) in the brimonidine + timolol group were discontinued from the study.

Conclusion: The efficacy of the dorzolamide/timolol combination and the concomitant administration of brimonidine and timolol were comparable. The incidence of drug-related adverse experiences and the incidence of discontinuations caused by drug-related adverse experiences were similar between groups.

Sall KN et al: Dorzolamide/Timolol Combination versus Concomitant Administration of Brimonidine and Timolol: Six-Month Comparison of Efficacy and Tolerability. Ophthalmology 2003;110(3):615-624.[34]

12-week study comparing COMBIGAN™ with concomitant use of the individual components in patients with glaucoma and ocular hypertension

Objective: To evaluate the efficacy and safety of COMBIGAN™ ophthalmic solution dosed BID and demonstrate non-inferiority to concomitant use of brimonidine tartrate 0.2% BID and timolol 0.5% BID in glaucoma and ocular hypertension patients with intraocular pressure (IOP) uncontrolled on monotherapy.

Methods: Randomized, multicenter, double-masked, parallel-group study involving 371 patients with inadequate IOP control (IOP from 22 to 34 mmHg) after ≥3 weeks of run-in on any monotherapy. Patients were treated with COMBIGAN™ BID (fixed-combination group, n=188) or concomitant brimonidine BID and timolol BID (concomitant group, n=183). IOP was assessed pre-dose and 2 hours after morning dosing at weeks 2, 6, and 12. The study was carried out at 22 centers in 7 countries.

Results: *Efficacy:* Study completion rates were high in both treatment groups (94.1% for the combination group and 97.3% for the concomitant group). Patients in the COMBIGAN™ group discontinued from the study due to adverse events (n = 4), loss to follow-up (n = 4), protocol violations (use of prohibited medication, n = 1), and other reasons (n = 2). Patients in the concomitant group discontinued from the study due to adverse events (n = 2), loss to follow-up (n = 1), protocol violations (use of prohibited medication, n = 1), and personal reasons (n = 1). In the ITT patient population with LOCF, both COMBIGAN™ ophthalmic solution and concomitant therapy provided statistically and clinically significant mean IOP reductions from monotherapy-treated baseline at each follow-up time point at each visit ($p<0.001$). There were no significant between-group differences in the mean change from baseline IOP.

Safety: COMBIGAN™ therapy and concomitant therapy showed similar safety profiles, and both were well tolerated. The overall incidence of adverse events, regardless of causality, was comparable between groups (30.3% in the COMBIGAN™ group and 24.6% in the concomitant group). Most adverse events were mild or moderate in severity. One or more treatment-related adverse events, identified by the investigator as possibly, probably, or definitely related to treatment, were reported for 20.2% of patients in the COMBIGAN™ group and 14.2% in the concomitant group ($p=0.126$). Ocular pain, ocular pruritus, and headache were the most commonly reported treatment-related adverse events. There were no significant between-group differences in the incidence of any particular adverse event.

Conclusion: The results of this study demonstrate that the COMBIGAN™ ophthalmic solution is as effective as concomitant therapy with brimonidine and timolol in reducing IOP in patients with IOP uncontrolled on monotherapy. The difference in efficacy, as measured by mean IOP and mean change from baseline IOP, between COMBIGAN™ and concomitant administration of the component drugs was consistently less than 1 mmHg. Further, COMBIGAN™ was safe and well tolerated, and it is conveniently dosed with a single drop twice daily. This simplified dosing regimen could have a positive effect on compliance.

Goni FJ, for the BRIMONIDINE/TIMOLOL FIXED COMBINATION STUDY GROUP: 12-week study comparing the fixed combination of brimonidine and timolol with the concomitant use of the individual components in patients with glaucoma and ocular hypertension. Eur J Ophthalmol 2005;15:581-90.[35]

A Comparison of Allergy Rates in Glaucoma Patients Receiving Brimonidine Monotherapy versus COMBIGAN™

Objective: To evaluate the incidence of topical allergy in patients treated with COMBIGAN™ compared to brimonidine 0.2% monotherapy.

Methods: Allergy rates were prospectively determined for the first 102 glaucoma patients prescribed COMBIGAN™ ophthalmic solution. None of the patients had previously used brimonidine in any form. The patients were assessed for rate of allergies at months 1, 3, 6, 12, and 15 of treatment.

Allergy was defined as the presence of follicles and redness severe enough to warrant discontinuation of the fixed combination. Itching alone ascribed to the drug in the absence of follicles and/or redness was not a reason for discontinuation. The incidence of itching alone was recorded. Allergy rates for brimonidine 0.2% monotherapy were determined by retrospective review of the first 102 patients treated within the first 15 months following the commercial release of brimonidine 0.2%. The same criteria for allergy were used in both groups.

Inclusion criteria: Primary open angle glaucoma (POAG) or exfoliation syndrome (PXE) and no previous exposure to brimonidine. Both COMBIGAN™ and the brimonidine 0.2% as monotherapy were prescribed as a BID dosage regimen.

Results: There were no statistical differences in the 2 groups with regards to age, gender or type of glaucoma. All patients either had primary open angle glaucoma or exfoliation syndrome.

The percentage of patients with allergies at month 15 using brimonidine was 15.7% versus 7.8 % using brimonidine/timolol fixed combination.

There were no differences in ophthalmic solution complaints of itching in the 2 groups. It is unclear why the allergy rate with COMBIGAN™ has shown clinically lower allergy rates than brimonidine 0.2% monotherapy.

Possible explanations for these findings include:

1. There is evidence suggesting that timolol's effect limits the allergic response in eyes treated with brimonidine.
2. Studies have demonstrated that adrenergic agents reduce the volume of conjunctival cells which widens the spaces between these cells. This could allow potential allergens to pass through and elicit a local allergic response. Timolol has been shown to block this widening effect.
3. Timolol's weak vasoconstrictive properties in some vascular beds may decrease signs and symptoms of inflammation.

Conclusion: IOP-lowering therapy with COMBIGAN™ ophthalmic solution is associated with clinically lower allergy rates than with brimonidine 0.2% monotherapy. The results of this trial should be validated with additional studies.

Motolko, MA et al: A Comparison of Allergy Rates in Glaucoma Patients Receiving Brimonidine Monotherapy versus Fixed Combination Brimonidine/Timolol Presented at the American Glaucoma Society Annual Meeting; 2006 Mar 2-5; Charleston NC.[36]

Comparison of COMBIGAN™ With Concomitant Use of the Individual Components in Glaucoma and Ocular Hypertension: Achievement of Clinically Relevant IOP Reductions

Objectives: To evaluate the additional IOP reduction achieved by patients who switch from monotherapy to COMBIGAN™ therapy or concomitant therapy with brimonidine and timolol.

Methods: Three-month, multicenter, randomized, double-masked, parallel-group clinical trial. Key inclusion criteria: Age ≥ 18 years with chronic open-angle glaucoma, chronic angle-closure glaucoma with a patent iridectomy, pseudoexfoliative glaucoma, pigmentary glaucoma, or ocular hypertension (OHT); IOP of 22-34 mm Hg in at least one eye after ≥ 3 weeks of bilateral monotherapy. COMBIGAN™ ophthalmic solution and vehicle BID to maintain masking. "Concomitant" therapy = 0.2% brimonidine tartrate ophthalmic solution BID and 0.5% timolol ophthalmic solution BID.

Efficacy Measure: IOP measured at 9:30 AM ± 1 hour (just before administration of study drugs) and 2 hours later at baseline and on weeks 2, 6, and 12.

Safety measure: Incidence of adverse events, vital signs, biomicroscopy, ophthalmoscopy, visual acuity, visual fields, and laboratory tests (hematology, chemistry, urinalysis).

Results: Patients inadequately controlled on monotherapy achieved statistically significant and clinically meaningful decreases in IOP when they were switched to either COMBIGAN™ or concomitant therapy. Average IOP reductions during follow-up ranged from 4.4-5.3 mm Hg in each treatment group. Over 60% of patients achieved at least a 15% IOP reduction from monotherapy-treated baseline after switching to COMBIGAN™ ophthalmic solution or concomitant therapy for 12 weeks. 29.3% of patients in the COMBIGAN™ group, achieved an average IOP ≤17.5 mm Hg over all follow-up measurements. Almost 1 out of 3 patients achieved an average follow-up IOP of ≤17.5 mm Hg when switched to COMBIGAN™, demonstrating that COMBIGAN™ provides IOP control for many patients who are uncontrolled on monotherapy. COMBIGAN™ ophthalmic solution was safe and well tolerated.

Conclusions: COMBIGAN™ provided clinically meaningful IOP reductions from monotherapy treated baseline and was as effective, safe, and well tolerated as concomitant therapy with the component drugs. The simplified dosing regimen is likely to improve patient compliance. COMBIGAN™ can be confidently used in place of dual, concomitant therapy with brimonidine and timolol.

Goni, FJ and Ingram AM, for the Brimonidine/Trimolol Fixed-Combination Study Group: Comparison of Fixed-Combination Brimonidine and Timolol With Concomitant Use of the Individual Components in Glaucoma and Ocular Hypertension: Achievement of Clinically Relevant IOP Reductions. Presented at the 5th International Glaucoma Symposium (IGS); March 30-April 2, 2005; Cape Town, South Africa. [37]

2.3 Outcomes Studies and Economic Evaluation Supporting Data

Pharmacotherapy Compliance and Glaucoma Surgery in Patients with Primary Open-Angle Glaucoma

Objectives: To determine the relationship between pharmacotherapy compliance and likelihood of glaucoma surgery in patients with POAG.

Methods: This study was a retrospective database analysis of a nationally representative, multi-managed care plan claims database (PharMetrics) for the years of 1996 to 2004. All statistical analyses were conducted using SAS Version 9.1. Patients ≥18 years of age with at least one ICD-9 diagnosis code for POAG, any medication for glaucoma (the first serving as index date), and a minimum of 1 year follow-up before and 2 years follow-up after index date were included.

Results: The study population included 3,864 POAG patients who met all inclusion criteria. Mean medication coverage was 0.47 (SD=0.26), meaning that patients were covered by any glaucoma medication for approximately 47% (172 days) of their first year of follow-up; median was also 0.47, and 75th percentile was 0.67. Unadjusted results demonstrated that patients with glaucoma surgery during the second year of follow-up had significantly higher mean compliance in the first year of follow-up when compared to patients without a glaucoma surgery during the second year (0.54 vs. 0.45 respectively, $p<0.0001$).

Although compliance was not significantly associated with surgery ($p=0.10$) in the logistic regression model controlling for key covariates, the trend of compliant patients being less likely to receive glaucoma surgery than non-compliant patients across models of varying severity was statistically significant ($p=0.02$). Using one glaucoma medication (compared to two or more) significantly lowered the likelihood of undergoing surgery ($p<0.01$) With increasing health severity, compliant patients were less likely to have had glaucoma surgery when compared to non-compliant patients; this trend was significant ($p=0.02$). Among the worst health severity group, compliant patients were almost two times less likely to have had glaucoma surgery than non-compliant patients. Among the best health severity group, compliant patients were more likely to receive glaucoma surgery. This may be attributed to patients with better health being more likely to go for surgery regardless of compliance (more related to how many medications they have used without adequate effect).

Conclusions: In POAG patients with increased health severity (defined by charges), improved compliance with pharmacotherapies was associated with a reduced likelihood of undergoing glaucoma surgery. Enhanced patient compliance with glaucoma medications (via the implementation of POAG treatment strategies) can reduce the odds of having glaucoma surgery. Further research is needed to obtain more specific glaucoma and/or ocular-health related charges so that the effects of POAG severity, specifically on glaucoma medication compliance, can be more closely examined.

Tsai JC et al: Pharmacotherapy Compliance and Glaucoma Surgery in Patients with Primary Open-Angle Glaucoma. Presented at The 2006 American Glaucoma Society Meeting; March 2-5, 2006; Charleston, SC.[38]

Does Adjunctive Glaucoma Therapy Affect Adherence to the Initial Primary Therapy?

Objectives: To examine the effect of adding complexity to a glaucoma medical treatment regimen – specifically, what would occur to the refill rate (and, any inference, to adherence) when a second medication was added to a currently used once-daily drug.

Methods: Open-label retrospective review of patient records. Patients of a large national health care provider who had received a prescription for latanoprost between July 1, 2001 and June 30, 2002. There were 1784 patients who had a second medication added and 3146 patients who remained on monotherapy. For each patient, the mean number of days between refills was calculated for both the period and that subsequent to the addition of the second medication, and an inter-period difference in refill interval between the 2 periods was calculated. Probability comparisons were performed using paired t tests (continuous) and Wilcoxon signed rank tests (categorical).

Results: In the population of 1784 patients who used 2 different ocular hypotensive medications, mean refill intervals were 40.6$\pm$21.8 days for latanoprost before the addition of a second drug and 47.4$\pm$24.4 days after the addition of a second drug, with a mean increase of 6.7$\pm$25.6 days. The 95% confidence interval for this mean increase of approximately 1 week was 5.6 to 7.9 days ($P<0.0011$). For 22% (409/1784) of patients, the interval was increased by >2 weeks ($P<0.0001$). The mean refill interval was longer than that for the 3146 patients who continued on latanoprost montherapy, which was 41$\pm$24 days.

Conclusions: A decrease in adherence associated with the addition of another therapy, irrespective of the size, frequency of administration, or type of adjunctive medication was found. In those patients who did not have an additional medication added and remained on latanoprost as their sole medication, no numerical difference of note in the refill rate among those continuing on latanoprost monotherapy and those who were originally on latanoprost before the addition of a second adjunctive medication was found. Treatment adherence is a critical factor in the success of glaucoma therapy. Improved adherence to medical therapy could result in considerable preservation of vision, and lower IOPs are associated with slower disease progression.

Robin AL and Covert D: Does Adjunctive Glaucoma Therapy Affect Adherence to the Initial Primary Therapy? Ophthalmology 2005;112:863-868.[14]

Patient-Reported Behavior and Problems in Using Glaucoma Medications

Objectives: To describe the different types of problems patients receiving adjunctive therapy reported having when taking their glaucoma medications and to examine the relationship between patient-reported problems in taking their glaucoma medications and patient adherence.

Methods: Cross-sectional survey. A survey was distributed to glaucoma patients in 4 geographically distinct ophthalmology practices taking more than one glaucoma medication. The survey was completed by 324 patients who had scheduled visits at participating practices during summer or fall of 2004. For each patient, average percent adherence to his or her glaucoma medication regimen was calculated. Logistic regression was used to examine how patient characteristics and problems in using glaucoma medications were related to reported adherence.

Main Outcome Measure: Whether patients were less than 100% adherent in the previous week.

Results: Sixty-two percent of patients expressed one or more problems with their glaucoma medications. The most commonly cited problems were difficulty with drop administration (44%), paying for the medication (41%), reading the print on the bottle (18%), side effects (16%), sqeezing the bottle (14%), difficulty getting the seal off (14%), and remembering to take the medication (12%). 13% of patients reported not always administering their own eye drops. Patients taking more glaucoma medications were more likely to have several different problems taking their eyedrops than patients taking fewer glaucoma medications. Poor adherence was most strongly related to whether patients reported having difficulty remembering to take their medications. Fourteen percent of patients reported being less than 100% adherent to their glaucoma regimen medications during the previous week. Patients who had difficulty remembering to take their glaucoma medications and those who reported that they had other problems or concerns with their glaucoma medications were significantly less likely to be 100% adherent.

Conclusions: Patient adherence to a glaucoma medication regimen could be improved among patients receiving adjunctive therapy. Ophthalmologists and their clinical colleagues should make sure to discuss the problems and concerns that patients may have in taking their glaucoma medications in an effort to improve adherence. Improving adherence to glaucoma medication regimens is important, and future research needs to be carried out in this area. Patient compliance is essential for effective medication intervention and for minimizing peripheral and central vision loss.

Sleath B et al: Patient-Reported Behavior and Problems in Using Glaucoma Medications. Ophthalmology 2006;113:431-436.[39]

Cost-Minimization Analysis of COMBIGAN™ in the Treatment of Primary Open Angle Glaucoma in Europe

Objective: To assess ease of use, dosing reliability, and daily treatment costs with currently existing fixed-combination therapies. Specifically, the study measured the number of drops contained in marketed bottles of fixed-combination therapies (Cosopt®, Xalacom®, and Combigan®), and estimated the average daily cost of treatment when bottles are used for 1 month (30 days) or until empty.

Methods: A cost-minimization analysis including drug costs and ophthalmologist visits (health care perspective) was carried out for Germany, United Kingdom and Switzerland.

Results: The 3-months costs for Germany were €129.33 using COMBIGAN™ ophthalmic solution or *Cosopt*® and €159.15 using brimonidine+timolol. The similar costs were in United Kingdom £264.00 (COMBIGAN™), £265.17 (brimonidine+timolol) and £264.15 (*Cosopt®),* whereas the costs for Switzerland were Chf 710 (COMBIGAN™), Chf745 (brimonidine+timolol) and Chf717 (*Cosopt®).* Including additional drug costs and visits, the annual costs rose in Germany to €425.13 (COMBIGAN™ or *Cosopt®),* and €544.41 (brimonidine+timolol), in United Kingdom to £510.00 (COMBIGAN™), £514.68 (brimonidine+timolol), and £510.60 (*Cosopt*®), and in Switzerland to Chf1,470 (COMBIGAN™), Chf1,611 (brimonidine+timolol), and Chf1,500 (*Cosopt*®).

Conclusion: COMBIGAN™ ophthalmic solution provided better cost value than brimonidine+timolol adjunctively. The use of COMBIGAN™ instead of brimonidine+timolol would potentially result in annual societal savings around €7.2 million in Germany, £200,000 in United Kingdom and Chf770,000 in Switzerland. COMBIGAN™ ophthalmic solution resulted in slightly lower health care costs when modeling equal effectiveness compared with *Cosopt*®.

Buchholz P et al: COMBIGAN-Cost Minimization Analysis of Brimonidine/Timolol Fixed Combination in the Treatment of Primary Open Angle Glaucoma in Europe. (abstract and poster presented at International Symposium on Ocular Pharmacology and Therapeutics; 2006 Mar 20-Apr 2; Berlin)[40]

Reliability of Dosing, Ease of Administration, and Daily Costs in Glaucoma Combination Therapy in Germany, Ireland, Switzerland, and the United Kingdom

Objectives: To assess ease of use, dosing reliability, and daily treatment costs with currently existing fixed-combination therapies.

Methods: Twelve bottles of each combination product were obtained at a pharmacy: 5-mL bottles of COMBIGAN™ ophthalmic solution (fixed-combination brimonidine 0.2%/timolol 0.5%); 5-mL bottles of *Cosopt*® (fixed-combination timolol 0.5%/dorzolamide 2%); 2.5-mL bottles of *Xalacom*® (fixed-combination latanoprost 0.005%/timolol 0.5%). Drop counts were performed by 3 ophthalmologists and 1 elderly glaucoma patient. Each participant counted the number of drops in bottles of COMBIGAN™ , *Cosopt*®, and *Xalacom*®, testing 3 bottles of each product (for a total of 9 bottles) and 1 bottle per day over a period of 9 to 10 days. Drug prices for each country were based on the pharmacy price (including value-added tax) of a package of 3 bottles, where available; otherwise the price of a single bottle was used. All prices were converted to euros to facilitate price comparison among countries. Daily treatment costs were estimated by dividing the cost of a bottle of medication by the number of days' treatment. In one analysis, the number of days' treatment provided by 1 bottle of each product was calculated as the estimated mean number of drops per bottle divided by the daily dosage required for bilateral treatment (2 drops/day for *Xalacom*® and 4 drops/day for COMBIGAN™ ophthalmic solution and *Cosopt*®). In a second analysis, each bottle of medication was assumed to provide 30 days of treatment.

Results: The mean number of drops dispensed per bottle was 164 for COMBIGAN™ , 169 for *Cosopt*®, and 86 for *Xalacom*®. Measures of variability in drop count (SD and 95% CI) were lowest for COMBIGAN™, suggesting that COMBIGAN™ provides the most reliable dosing. The SD of the mean drop count was 4.0 for COMBIGAN™ ophthalmic solution, 14.4 for *Cosopt*®, and 7.9 for *Xalacom*®. Using the mean drop count, the number of bilateral treatment days provided by a bottle of medication can be estimated as: 41.0 days per 5-mL bottle of COMBIGAN™ (BID dosing); 42.3 days per 5-mL bottle of *Cosopt*® (BID dosing); 42.9 days per 2.5-mL bottle of *Xalacom*® (QD dosing).

COMBIGAN™ and *Cosopt*® were generally similar in price. In Germany and the United Kingdom, the price of *Cosopt*® was within 1% of the price of COMBIGAN™ ophthalmic solution. In Ireland and Switzerland, the price of *Cosopt*® was 6% to 16% higher than the price of COMBIGAN™. *Xalacom*® had the highest price in all 4 countries. In Germany, the price of *Xalacom*® was 11% higher than the price of COMBIGAN™ ophthalmic solution. In Ireland and the United Kingdom, the price of *Xalacom*® was 51% to 58% higher than the price of COMBIGAN™ ophthalmic solution. In Switzerland, the price of a package of 3 bottles was 51% higher for *Xalacom*® than for COMBIGAN™ .

The mean daily cost of treatment was highest for *Xalacom*® in all 4 countries. Mean daily cost of treatment was 6%, 52%, 44%, and 44% higher with *Xalacom*® than COMBIGAN™ ophthalmic solution in Germany, Ireland, Switzerland, and the United Kingdom, respectively. Mean daily cost of treatment was 10%, 33%, 35%, and 49% higher with *Xalacom*® than *Cosopt*® in Germany, Ireland, Switzerland, and the United Kingdom, respectively. The mean daily cost of COMBIGAN™ treatment was lower than the mean daily cost of *Cosopt*® treatment

in 2 countries. Daily treatment costs were 12% lower with COMBIGAN™ than with *Cosopt*® in Ireland and 7% lower in Switzerland. In Germany and the United Kingdom, the mean daily cost of COMBIGAN™ treatment was within 3% of the mean daily cost of *Cosopt*® treatment. Use of ophthalmic multidose bottles is limited to 1 month of treatment in Europe. Similar results were observed when the cost analysis assumed that bottles were used for 30 days only. The daily cost of treatment was consistently highest with *Xalacom*® in all 4 countries.

Conclusions: COMBIGAN™ ophthalmic solution provides the most consistent number of drops per bottle and the highest dosing reliability. *Xalacom*® is the most expensive fixed-combination treatment in all 4 countries. COMBIGAN™ is the least expensive treatment in Ireland and Switzerland and is comparable in daily cost to *Cosopt*® in Germany and the United Kingdom.

Buchholz AP and Tan M: Reliability of Dosing, Ease of Administration, and Daily Costs in Glaucoma Combination Therapy in Germany, Ireland, Switzerland, and the United Kingdom. Poster presented at 104th German Ophthalmological Society (DOG) Annual Meeting; September 21-24, 2006; Berlin, Germany.[41]

Cost considerations of the new fixed combinations for glaucoma medical therapy

Objectives: To compare the costs of the new fixed combinations for glaucoma medical therapy.

Methods: The studied drugs were: *Cosopt*® (5-mL bottle), COMBIGAN™ (5-mL bottle) and *Xalacom*® (2.5-mL bottle). Five bottles of each drug were obtained from pharmacies, and the medications lot numbers were recorded. To calculate the drop volume, 10 drops and 1 mL of each bottle were weighed with a digital precision scale. Drop volume was calculated by the relation between volume and weight. The cost of each bottle of medication was determined from the average retail price in Canada. The prices were obtained in Canadian dollars ($).

Results: The drops of *Cosopt*® (39.60 ± 0.45 μL) were considerably larger than the drops of COMBIGAN™ ophthalmic solution (33.75 ± 0.60 μL) and *Xalacom*® (30.87 ± 0.37 μL). The average number of drops per milliliter varied from 25.25 ± 0.29 (*Cosopt*®) to 32.40 ± 0.39 μL (*Xalacom*®). COMBIGAN™ presented the lowest daily cost ($0.87 ± 0.02) followed by *Xalacom*® ($1.09 ± 0.01) and *Cosopt*® ($1.22 ± 0.01). The average cost by year varied from $316.75 ± 5.59 (COMBIGAN™) to $445.96 ± 5.16 (*Cosopt*®), with a total difference of $129.21 per year of treatment.

Conclusions: In regards to efficacy and safety, according to the literature, there are no marked differences among the studied medications therefore cost should be considered in deciding which medication to prescribe. Final cost of therapy may be based on several factors beyond that of the retail price and include the drop size and the amount of drops per bottle. There was a statistically significant difference in average drop size and cost among the three studied drugs. COMBIGAN™ ophthalmic solution presented the lowest daily cost followed by *Xalacom*® and *Cosopt*®. The annual cost differential was approximately $ 130 between COMBIGAN™ and *Cosopt*®. Finally, the medication cost is a reflection of multiple factors including the retail price, amount of medication per bottle, the drop size, and optimal dose. The results of this study suggest that marked differences exist in cost among the new Fixed Combinations for glaucoma medical therapy.

Ventura MP et al: Cost considerations of the new fixed combinations for glaucoma medical therapy. J Clin Pharm Ther. 2005;30:251-254.[42]

2.3.1 Quality of Life Data

There are no data available on quality of life in glaucoma patients treated with COMBIGAN™ using an established, validated quality of life instrument. The pivotal Phase III study which examined COMBIGAN™ ophthalmic solution versus the individual components adjunctively, also included a placebo arm in the combination group in order to blind the study. Therefore, the potential advantages of convenience and ease of administration for the patient could not be measured.[12, 19-23]

In one recent study where the primary outcome measure evaluated was patient satisfaction, it is most interesting to note the percentages in the sub-analysis of patients who switched from *Cosopt*® monotherapy to COMBIGAN™ monotherapy (n= 80, monotherapy n= 25),. In comparing the two monotherapies, the patient evaluation results showed that 80% of patients said they were more satisfied with COMBIGAN™ ophthalmic solution than they were with *Cosopt*®; 88% found that COMBIGAN™ was more convenient; and 92% of patients determined that the ocular comfort of COMBIGAN™ was superior to that of *Cosopt*®.[27]

Of secondary outcome measures, reports of adverse events were infrequent (13%); of those, the majority were mild-to-moderate and transient, and/or resolved once medication was discontinued.[30]

The remaining secondary outcome measure evaluated physician satisfaction (n = 47). Rating COMBIGAN™ overall (as either monotherapy or add-on therapy), 96% said they felt COMBIGAN™ ophthalmic solution met or surpassed their expectations; 98% found COMBIGAN™ to be good or excellent as compared to other IOP-lowering agents; and all physicians indicated that they would prescribe COMBIGAN™. [27]

Fixed-combination agents offer benefits such as decreased preservative, convenience, compliance, improved cost, and safety. COMBIGAN™ ophthalmic solution is both an efficacious and well tolerated combination agent, and one that should be considered in patients who would potentially benefit from its effectiveness and patient tolerability as well as those who would prefer the convenience of a single-bottle solution — thereby improving ease of use, and perhaps may improve patient compliance.[27]

2.3.2 Planned Studies

Authors	Working Title	Approximate Timeline
Franks, W.	COMBIGAN™ vs. *Cosopt*®: IOP lowering of an established second line agent Cosopt versus the efficacy of a newly available second line agent COMBIGAN™ - A prospective parallel double masked study	Publication planned (Q2 08)
Hommer A, Wickstrøm J, Friis MM, Buchholz P, Walt JG, Poulsen PB	A European perspective on costs and cost-effectiveness of ophthalmic combinations in the treatment of glaucoma.	In progress (Q2 08)
Nixon, DR	Evaluation of the Tolerability and Efficacy of Brimonidine Tartrate-Timolol Maleate Ophthalmic Solution (COMBIGAN™) and Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution (*Cosopt*®) in Patients with Open-Angle Glaucoma or Ocular Hyperemia	In progress (Q4 08) Presented as a poster at the American Glaucoma Society (AGS) 2007 Annual meeting and the American Academy of Ophthalmology (AAO) 2007 Annual meeting
Susanna, R.	COMBIGAN™ Vs. *Cosopt*® - Water Drinking Study	Publication planned
	CEED COMBIGAN™ PMS Australia	Publication planned (Q3 08)

3 IMPACT MODEL REPORT

3.1 Overview

3.1.1 Background

Primary open-angle glaucoma is estimated to affect more than 2.2 million individuals in the U.S.,[6] with a prevalence of 1.86% in the population over 40 years of age.[6] One study estimated the total direct medical cost of glaucoma in the US to be $2.9 billion.[43] Regardless of glaucoma severity, medication for treating the disorder has been associated with at least 48% of direct healthcare costs among fully compliant patients. When more conservative compliance estimates were used, medication comprised 38% to 44% of direct glaucoma costs.[44] As members of the aging population are increasingly diagnosed with glaucoma, the overall costs associated with the disorder, including the direct medication costs, are expected to rise.

3.1.2 Objectives

The primary purpose of this pharmacoeconomic assessment of COMBIGAN™ ophthalmic solution is to assist in making efficient healthcare decisions and to aid in the delivery of cost-effective healthcare. A budget impact model was developed to examine the economic consequences of adding COMBIGAN™ to a health plan formulary in order to consider its use in glaucoma patients. It was developed as a pharmacoeconomic tool for managed care organizations to optimize cost-effectiveness among glaucoma agents.

In clinical trials, the efficacy profile of COMBIGAN™ ophthalmic solution has been established.. The conservative approach to economic assessment, therefore, would be to use a cost-minimization approach. When examining the glaucoma category from a cost-minimization perspective, the primary difference in this class is the actual acquisition cost per unit of medication. The purpose of the enclosed budget impact model is to compare the cost of all current major glaucoma agents, including: ALPHAGAN® P ophthalmic solution, generic brimonidine, timolol, *Timoptic*®, other beta-blockers [*Betoptic*® *S* (betaxolol), BETAGAN® (levobunolol), *Ocupress*® (carteolol), *Optipranolol*® (metipranolol)], *Azopt*™, *Trusopt*®, *Cosopt*®, LUMIGAN® ophthalmic solution, *Travatan*®, *Xalatan*®, and COMBIGAN™.

3.1.3 Assumptions

- This budget impact analyses only considers pharmacy costs.
- The timolol category of glaucoma medications includes: timolol maleate GFS, timolol maleate oph, *Betimol*®, *Timoptic*®, and *Timoptic*® *Ocudose*; the Timpotic category includes: *Timoptic*® *XE*; and the other beta-blockers includes: *Betoptic*® *S* (betaxolol), BETAGAN® (levobunolol), *Ocupress*® (carteolol), *Optipranolol*® (metipranolol).

- In the current model, a 5 mL supply is predicted to last for one full month of treatment except for the lipids in which a 2.5ml bottle lasts for one full month. The number of prescriptions per patient per year is set to 12 and is customizable by the user. RR factors derived from the literature are used to calculate differences in cost due to utilization patterns and prescription refills of 10 mL and 15 mL bottles.[45]
- Prices for the beta-blocker medications are weighted averages of brand name or generic maximum allowable cost (MAC) prices of 5 mL bottle sizes.
- The AWP per month for all other glaucoma medications is a weighted average of a one-month supply of all of the medications in that category for a 5 mL bottle.
- The model calculates the wholesale acquisition cost (WAC) assuming a flat 20% reduction from AWP.
- Current market size is applied to future scenario analyses, users have the option to assume that COMBIGAN™ ophthalmic solution will take its entire market exclusively from *Cosopt*®, exclusively from combinations of brimonidine and timolol, or proportionally from all three medications or as defined by the user. Users also have the option of directly adjusting the market share in the future scenario analyses and the default is set at a distribution of market shares based on internal Allergan predictions.
- Users have the option to assume that the number of eligible patients in the plan is proportional to the covered lives population as compared with medication in the covered lives population.

3.1.4 Model Structure

The model estimates the impact of adding COMBIGAN™ to the formulary at the patient-level as well as at the level of the plan's budget, based on the current market share of total prescriptions in this category. Average wholesale prices (AWP) and wholesale acquisition costs (WAC) were computed as a weighted average of all dosage sizes of each product. Patient-level analyses were performed by summing up pharmacy costs and, where appropriate, rebates, discounts, and copays over a one-month period and extrapolating results for a one-year period.

The model provides two options for performing economic assessments at the population level: (1) covered lives approach and (2) treated prevalence approach. The covered lives approach includes a cost assessment for an assumed number of covered lives in a plan. Alternatively, if reliable plan-specific epidemiology and utilization data is available, plan-specific cost assessment can be performed with the treated prevalence approach.

The model also provides the option to perform simulations of results of utilization programs adopted by the health plan. For example, payers can assume a scenario in which COMBIGAN™ ophthalmic solution will take market share from either the current market leader in combination therapy (*Cosopt*®), from the two individual components of COMBIGAN™ (brimonidine and timolol) or proportionally from *Cosopt*®*,* brimonidine, and timolol.

The model has been developed using national data, but the user can vary the inputs to the model and generate specific scenarios using plan specific epidemiology, utilization, and cost data. Entries of individualized cost data in the *Rx and Cost Data* fields help to more accurately

simulate the actual cost of treatment within each plan. Adjustment of market shares in the fields of *Utilization Characteristics* allows the user to model a base or current case versus a future case. These adjustments allow the user to evaluate the impact that changing market shares has on the managed care organization's budget.

3.1.5 Results

In order to examine the economic consequences of adding COMBIGAN™ ophthalmic solution to a health plan formulary, results of the simulations were demonstrated at the patient-level by comparing the cost of treatment with COMBIGAN™ to other products over a 12-month period. A cost-minimization model was used to predict the glaucoma pharmacy expenditures of a health plan. These effects were translated into overall cost, per prescription cost, per patient cost and per member cost, as shown in the *Budget Impact Summary*.

3.2 Parameter Estimates

The model uses published medication costs[46] and market share data.[47,48] The cost-minimization model assumed a hypothetical health plan of 1,000,000 covered lives. The total number of annual glaucoma prescriptions in this plan was estimated based on the proportion of its covered lives to national population, or the proportion of its number of treated patients to the national parameter.

Covered lives scenario:

$$Plan\ \ Total\ \ Annual\ Rx\ =\ \frac{National\ Total\ \ Annual\ Rx\ \times\ Covered\ Lives}{National\ Population}$$

Treatment prevalence scenario:

$$Plan\ Total\ \ Annual\, Rx\ =\ \frac{National Total\ \ Annual\, Rx\ \times\ \ Number of\ \ \ Patients Treated in\ \ Plan}{Number of\ \ \ Patients Treated\, Nationally}$$

3.3 Perspectives and Time Horizon

The model was constructed from the perspective of a managed care plan. The results, therefore, are presented in terms of the annual cost of treatment per patient, as well as the annual plan net pharmacy cost and per member pharmacy cost. Values are based on total expected cost over 12 months and the use of drug alone over the same length of time. Assuming the market growth is driven by the increasing awareness of seeking medical treatment, national market forecasting was performed based on the trend of current market growth since 2006.

3.4 Presentation of Results

In the patient-level analyses, the model compares the total annual net cost of treatment of glaucoma per patient using COMBIGAN™ ophthalmic solution and other glaucoma drugs.

Based on the attached budget impact model, patients treated with COMBIGAN™ will cost $559.75 per year, compared with $537.92 for treatment with *Cosopt*®, $290.91 for treatment with brimonidine, $106.57 for treatment with timolol, and $425.00 for the glaucoma category mean.

In the cost-minimization model, results are reported as overall costs to the plan for glaucoma agents, as well as per prescription costs, per patient costs and per member costs, shown in the *Budget Impact Summary*. For assumed 1,000,000 covered lives, the prevalence of glaucoma has been estimated at 1.0% and the proportion of patients receiving treatment has been estimated at 50.6%, in concordance with national estimates obtained from published literature.[52]. Given the assumed 1.5% market share that COMBIGAN™ would take from its competitors in the first year, the annual total pharmacy cost change to the plan for glaucoma agents would be $219,681 after adding COMBIGAN™ ophthalmic solution to its formulary. The overall annual cost change per prescription, thus, is $2.96, which translates into a per patient cost change of $43.42, a per member per year cost change of $0.22, and a per member per month cost change of $0.018. In a future year, where the market share of COMBIGAN™ is expected to reach 2.9%, total pharmacy cost change to the plan for glaucoma agents would be $205,036 with COMBIGAN™ on formulary. In this future scenario, the overall annual cost change per prescription is $2.76, which translates into a per patient cost change of $40.52, a per member per year cost change of $0.21, and a per member per month cost change of $0.017.

COMBIGAN™ has proven efficacy in reducing IOP. The addition of COMBIGAN™ ophthalmic solution to a health plan's formulary would have a small impact on the plan's overall budget for glaucoma agents. Given the single therapy advantage of COMBIGAN™ and its small budget impact, COMBIGAN™ would be a good candidate for addition to glaucoma formularies.

4 PRODUCT VALUE AND OVERALL COST

COMBIGAN™ ophthalmic solution provides safe, powerful and effective IOP reduction in patients with glaucoma or OHT who require adjunctive or replacement therapy due to inadequately controlled IOP.

COMBIGAN ™ has a dual mechanism of action thereby reducing aqueous humor production and increasing nonpressure dependent uveoscleral outflow.[1, 2]

COMBIGAN™ is a safe and effective therapy for lowering IOP in patients with open angle glaucoma or ocular hypertension.[19,22,23,25,26]

COMBIGAN™ ophthalmic solution has additional IOP lowering efficacy compared to brimonidine 0.2% and to timolol 0.5% used individually as monotherapy. [19,22,23,25,26]

COMBIGAN™ has an acceptable safety profile and showed no difference in adverse event profile compared to the active components administered individually and a low allergy rate (5.2% in 385 COMBIGAN™ patients).[50,37, 24,12,20,21,27,35]

With COMBIGAN™, achievement of target pressures ≤ 18 mm Hg increased from 31% at treated baseline to 70% by 2 months[27]

Overall, 68% of COMBIGAN™ treated eyes achieved greater than 15% reduction in IOP from treated baseline[27]

COMBIGAN™ ophthalmic solution is a powerful adjunct to prostaglandin therapy and a valuable alterative for patients on a beta-blocker who need additional IOP reduction

COMBIGAN™ reduced mean IOP up to 29% at three months when added to PGA therapy at baseline ($p<0.001$)[26]

COMBIGAN™ is a valuable alternative for patients who need additional IOP reduction on a beta-blocker. [35,40-43,51]

COMBIGAN™ reduced mean IOP up to 25% at 3 months in patients switched from timolol at baseline. [35,40-43,51]

The addition of COMBIGAN™ ophthalmic solution is a cost effective combination glaucoma therapy and would have minimal budget impact to a health plan's formulary

Patients on COMBIGAN™ administer fewer drops daily than with adjunctive therapy. [50,37, 24,12,20,21,27,35]

COMBIGAN™ provides the same level of safety and efficacy but in the convenience of a single bottle. The benefits are better convenience which may improve compliance for the patients. Better compliance may lead to better IOP control.[14-16,38,45]

Compared to the individual components administered alone or adjunctively, COMBIGAN™ ophthalmic solution does not have a negative effect on the patient's satisfaction with their treatment or the level of comfort of the drops providing patients with a greater opportunity to remain compliant. [50,37, 24,12,20,21,27,35]

COMBIGAN™ is cost-effective over timolol and brimonidine administered adjunctively. The price of COMBIGAN™ is less than the price of timolol 0.5% and brimonidine 0.2% administered adjunctively. [40-43,51]

Furthermore, COMBIGAN™ ophthalmic solution is more cost-efficient as compared to Cosopt® given a 5mL vs. only a 10mL size for their first month of therapy.

COMBIGAN™ ophthalmic solution has better tolerability than *Cosopt*®

When switched from *Cosopt*® to COMBIGAN™ therapy: The percentage of eyes achieving target pressures ≤ 18 mm Hg more than doubled from 29% to 64%. [27]

On measures of patient satisfaction, convenience, and ocular comfort, 80%, 88%, and 92% of respondents preferred COMBIGAN™ over *Cosopt*® in those respective measures. (n= 80, monotherapy n= 25). [27]

COMBIGAN™ patients (n=85) reported significantly less stinging (P = 0.001), burning (P = 0.0149), and unusual taste (P = 0.0047) than *Cosopt*® (N=86).[26]

Patients reported that COMBIGAN™ was significantly more comfortable than *Cosopt*® (P<.001). [26]

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ATTACHMENTS

5.1 Attachment 1: Clinical Evidence Tables

5.2 Attachment 2: Budget Impact Model

6 FORMULARY SUBMISSION CHECKLIST

6.1.1 Submission Process

1. Have you ever met with [PLAN NAME] staff to review the submission process?	❑ Yes	❑ No
2. Have you agreed to the submission date [PLAN NAME]	❑ Yes	❑ No
3. Have you requested summary data to identify baseline characteristics of the plan population?	❑ Yes	❑ No
4. Have you included an explanation for a missing data?(Check yes if not applicable)	❑ Yes	❑ No

6.1.2 Product Information

1. Have you provided a product description for the product?	❑ Yes	❑ No
2. Have you provided a list of approved indications for the product?	❑ Yes	❑ No
3. Have you identified the place of this product in therapy for each indication?	❑ Yes	❑ No
4. Have you provided copies of treatment guidelines for this product?	❑ Yes	❑ No
5. Have you listed the intermediate and final outcomes of therapy for this product?	❑ Yes	❑ No
6. Have you listed any co-prescribed drugs for this product by indication?	❑ Yes	❑ No
7. Have you identified the comparator drugs for this product by indication?	❑ Yes	❑ No

6.1.3 Supporting Clinical Information

1. Have you identify all relevant clinical and other experimental studies for the product?	❑ Yes	❑ No
2. Have you identified all relevant clinical and other experimental studies for the product's comparator therapies?	❑ Yes	❑ No
3. Have you included copies of all studies identified in the submission package?	❑ Yes	❑ No
4. Have you provided a spreadsheet summary of all studies identified?	❑ Yes	❑ No
5. Have you translated the outcomes to effectiveness terms?	❑ Yes	❑ No
6. Have you included these translations in the submission?	❑ Yes	❑ No
7. Have you included all relevant non-experimental studies for the product?	❑ Yes	❑ No
8. Have you included all relevant non-experimental studies for its proposed comparator therapies?	❑ Yes	❑ No
9. Have you provided a spreadsheet summary of all non-experimental studies?	❑ Yes	❑ No
10. Have you translated the outcomes in non-experimental studies to effectiveness terms?	❑ Yes	❑ No
11. Have you included these translations in the submission?	❑ Yes	❑ No

6.1.4 Supporting Economic Information

1. Have you identified all relevant pharmacoeconomic (PE) studies for the product?	❑ Yes	❑ No
2. Have you justified the relevance of these PE studies for this population?	❑ Yes	❑ No
3. Have you provided a spreadsheet summary of these PE studies, detailing their relevance?	❑ Yes	❑ No
4. Have you developed a therapy intervention framework for this product for each indication?	❑ Yes	❑ No
5. Have you confirmed the therapy intervention framework with the health plan?	❑ Yes	❑ No
6. Have you identified the characteristics of patients to be switched to this product?	❑ Yes	❑ No
7. Have you identified the patient characteristics that would exclude patients from your drug?	❑ Yes	❑ No
8. Have you provided electronics copies of all spreadsheet or models used?	❑ Yes	❑ No
9. Will a disease or care management strategy be utilized with the introduction of this product?	❑ Yes	❑ No
10. Have you included documentation on this intervention program in the submission?	❑ Yes	❑ No

6.1.5 Impact Model Assessments Costs

1. Have you included a baseline prevalence analysis of resource utilization and cost?	❑ Yes	❑ No
2. Have you structured these baseline estimates in terms of your therapy intervention framework?	❑ Yes	❑ No
3. Have you detailed the scenarios for cost impact assessment?	❑ Yes	❑ No
4. Have you highlighted the assumptions made for projecting patient switching behavior?	❑ Yes	❑ No
5. Have you justified the scenarios and assumptions for this plan's patient population?	❑ Yes	❑ No
6. Have you provided aggregate cost impact assessments for the 3 next years?	❑ Yes	❑ No
7. Have you provided a breakdown of the costs by medical resource utilization and drug categories?	❑ Yes	❑ No
8. Have you included a proposal on how these cost impact projections might be monitored?	❑ Yes	❑ No
9. Have you explained how differences between projections and actual costs might be resolved?	❑ Yes	❑ No
10. Have you included the cost of your proposed intervention program in the cost assessment.	❑ Yes	❑ No

6.1.6 Clinical

1. Have you included a baseline prevalence analysis of patient outcomes?	❑ Yes	❑ No
2. Have you structured these baseline estimates in terms of your therapy intervention framework?	❑ Yes	❑ No
3. Have you detailed the scenarios for outcome impact assessment?	❑ Yes	❑ No
4. Have you detailed the assumptions made for projecting patient switching behavior?	❑ Yes	❑ No
5. Have you justified the scenarios and assumptions for this plan's population?	❑ Yes	❑ No
6. Have you provided aggregate patient outcome impact assessments for the next 3 years/	❑ Yes	❑ No
7. Have you included a proposal in how patient outcomes might be monitored?	❑ Yes	❑ No
8. Have you explained the differences between the projected and actual patient outcomes?	❑ Yes	❑ No

7 AGENDA FOR PRE-SUBMISSION MEETING

7.1 List of intended indications

7.2 Summary of all studies to be included in the formulary submission.

- Clinical trials (experimental and non-experimental)
- Outcomes studies
- Meta Analysis
- Retrospective studies
- Pharmacoeconomic models

7.3 A general description of cost and outcomes impact assessments

- List of data sources (studies, database, etc.)
- Discussion of conversion of efficacy to effectiveness for both drug and comparators,
- Approach to modeling the environment of the health plan,
- Assumptions and suggested approach for determining patient characteristics for switching.

7.4 Summary of anticipated studies to be completed within 1-3 years